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UNRUPTURED INTERSTITIAL PREGNANCY*

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THE first recorded operation in America for ectopic pregnancy was reported by John Bard[1] in 1764. Subsequent operations followed in 1791 and 1799 and then almost a quarter of a century passed before the procedure was repeated in this country by Dr. Wishart, Oct. 6, 1823. Three varieties of extrauterine pregnancy were recognized, namely, tubal, ovarian, and abdominal. Breschet,[2] in 1826, added what he believed to be a new form, the interstitial type, although Schmitt[3] is generally credited with publishing the first authentic case of this variety. From the time of this latter report in 1801 and the first American paper on the subject by Fitz[4] of Boston in 1875, to the first operation for an interstitial pregnancy by Traub[5] in 1893, the historical chronology of the subject presents many interesting facts, all of which, collectively, prove the relatively rare occurrence of the interstitial implantation. Mathieu[6] stated that prior to 1893 interstitial pregnancy was recognized only at autopsy. Before that date, Fitz[4] in 1875 recorded 18 cases, Waegli[7] 53 in 1915, Moore[8] 79 prior to 1922 and Wynne[9] 140 in 1919. Ash[10] in his publication of 1932 stated that "there were only about 200 reported cases that could withstand critical analysis."

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Wynne[11] subsequently reviewed the data of 2,405 ectopic pregnancies and found only 40, or 1.66 per cent, of the interstitial type. Werth[12] reported 120 operations for ectopic pregnancy without finding a single case of this variety. Martin[13] found one in 77 and Munro-Kerr[14] also one in 80 ectopic pregnancies. Rosenthal[15] reviewed 1,300 cases of extrauterine pregnancy and found 3 per cent to be interstitial. The Johns Hopkins Hospital reports an incidence of 0.65 per cent. Ballantyne and associates[16] state that the incidence of interstitial pregnancy varies from 0.96 per cent to 2 per cent of all extrauterine pregnancies. This review clearly demonstrates that the interstitial type is a rare form, among which a correct preoperative diagnosis of an unruptured sac is still more infrequent. Cases following previous salpingectomy are still rarer. D'Errico[17] in 1937 correlated 23 such reported cases including his own. No reason for the salpingectomy was given. Richardson[18] in 1930 reviewed 9 cases in which tubal pregnancy was the reason for the salpingectomy performed.

Case Report

Mrs. E. C., was referred to me Jan. 10, 1952, complaining of amenorrhea of nine weeks' duration, intermittent severe lower abdominal pains for two months, and a moderate vaginal discharge. She was 32 years of age, married, and a housewife. Two previous pregnancies had resulted in children, one 6½ years of age the other 3½ years. She had had two spontaneous miscarriages, one at 3½ months, the other 2½ months. The last menstrual period was Oct. 25, 1951.

Since Nov. 17, 1951, there had been recurrent lower abdominal pains, which recently became more frequent and of increasing severity. Two days before the pains were well localized in the left lower quadrant of the abdomen, sharp, almost laborlike, and intermittent; occasionally these pains were referred to the back. There was no pain on urination or defecation. Three weeks before she had a slight vaginal spotting which lasted about one day, but did not recur.

On physical examination the patient showed no evidence of discomfort. The general physical examination was essentially negative, except for positive signs of pregnancy. No irregular masses were palpable on either side of the uterus suggestive of extrauterine pregnancy. The impression at the time was an intrauterine pregnancy and the cause of the severe intermittent pains undetermined.

The patient returned January 11 for check-up and stated that since her previous visit on January 8, she had several attacks of very severe pain. They were still localized in the left side and laborlike in character, but now she was comfortable. Pelvic examination was again essentially negative. While still at my office and just prior to her departure, the patient had an attack identical in character to those she had previously complained of. On pelvic re-examination, the uterus was found to be hard, irregular, with a protruding mass on the right side. The adnexa were negative and no vaginal bleeding was present. The attack lasted 8 to 10 minutes. A tentative diagnosis of interstitial pregnancy was made and the patient advised to enter the University Hospital immediately; she was admitted the same afternoon. Pelvic examinations late in the afternoon and also the next day failed to reveal the mass previously described. The patient had been practically symptom free since her admission to the hospital.

Two days later the patient had two attacks of pain during the early morning. The lower abdomen was slightly tender. There was no vaginal bleeding. On pelvic examination, the uterine irregularity was again found, suggesting the previous diagnosis of interstitial pregnancy; preparations were made for operation.

During the patient's stay in the hospital, the general laboratory findings showed nothing unusual except for a positive Aschheim-Zondek test and a mild anemia.

Operation.—A midline incision was made below the umbilicus and the peritoneal cavity entered. The uterus was found enlarged to about the size of a 2½ months' pregnancy, soft and globular. The adnexa appeared normal. Nothing could be found to account for the symptoms complained of. A thorough exploration of the pelvic and abdominal structures revealed nothing, except that the right kidney was rotated somewhat anteriorly. The patient was placed in an exaggerated Trendelenburg position and the appendix was removed.

Feeling that I might have missed something, I again thoroughly examined the pelvis. During this procedure, the uterus suddenly contracted to about two-thirds of its previous size; it became irregular with the left side firm and smooth, while the right showed an enlargement, soft, almost spongy in character, just medial to the insertion of the right Fallopian tube. The uterus except for the enlargement, had a mottled appearance.

The diagnosis of interstitial pregnancy was substantiated.

An incision was made in the lateral wall of the uterus, over the mass. The uterine wall in this area was less than one-half inch in thickness, and very soft. While the uterus was being incised, the placenta appeared in the wound. The opening in the uterus was enlarged and the products of conception removed. Repair was completed with the introduction of interrupted sutures to control bleeding. The patient made an uneventful recovery and was discharged from the hospital on the seventh day after operation.

In a review of the case just described, several salient factors can be selected and advantageously discussed. While some have been mentioned by various authors, their significance and importance have not been sufficiently stressed.

Pain as a symptom of interstitial pregnancy is a very important aid in diagnosis. It is intermittent in character, irregular in type, very severe, simulating labor pains and localized in the lower abdomen. It has been described as agonizing. In the interval, the patient is symptom free but ever subject to recurring attacks. In an endeavor to expel the misplaced growing ovum now acting as a foreign body, the uterus contracts intermittently, producing the characteristic laborlike pains. As the contractions subside and the uterine musculature relaxes, the uterus takes on the general contour of an intrauterine pregnancy. Due to the circular disposition of the muscle fibers of the cornu, distensibility is facilitated, so that the ovum may attain the size of a five months' pregnancy before rupture occurs.

It is conceded that in interstitial pregnancy the detection of a mass in the lateral wall of the uterus is extremely difficult, the more so when it is relaxed between attacks. Obviously the most opportune time for examination is either during an attack or immediately after. This is very well illustrated in our case. Vaginal bleeding may or may not be present.

During laparotomy for suspected interstitial pregnancy, the uterus may be found normal in contour, soft, globular, and corresponding in size to the existing stage of pregnancy. The uterine relaxation might probably be due to the degree of anesthesia administered. On pelvic exploration nothing may be found to account for the pre-existing symptoms. As a useful differential diagnostic aid in these circumstances, I would suggest massage of the uterus or injection of a minimum of Pituitrin or Ergotrate to produce uterine contraction. This would reveal the irregular uterine contour and enlargement at the cornu, indicative of interstitial pregnancy. I believe that this procedure, if followed, would remove uncertainty in diagnosis and the possibility of subsequent uterine rupture should the abdomen be closed without the existence of an interstitial pregnancy having been excluded.

In a certain number of cases it is possible to incise the uterus over the mass and remove the products of conception through this opening. This is a simpler procedure causing less tissue trauma and destruction than cornual excision.

Emerging from the lateral angle of the fundus uteri in the immediate vicinity and just above the uterine attachments of the uterovarian and round

ligaments, the first part of the tube is narrow and comparatively straight.[19] This constitutes the isthmus, about 3.4 cm. in length and from 3 to 4 mm. in diameter.

At the three angles of the uterine body corresponding to the two tubal orifices and the internal os, the arrangement of the fibers of the inner muscular layer suggests the existence of distinct sphincters. This sphincteric arrangement may be a factor in the arrest of the ovum. That part of the tube which traverses the uterine musculature constitutes the true interstitial portion. In other places the innermost muscular bundles are less regularly disposed and are oblique or even longitudinal. According to Ash,[10] the interstitial segment is relatively short. This segment may take a straight course. More commonly, it has an arc, with the curve toward the upper and posterior levels of the cornu. Or may contain sharp kinks.

The mucous membrane is smooth, thin, and without folds. When the ovum becomes arrested in this location, it lies almost in direct contact with the surrounding uterine muscle. Hence, when rupture takes place, there is no obstruction to its direct passage between the intermuscular spaces.

When implantation occurs, subsequent growth and development erode the thin mucosa and allow the ovum to become imbedded in the myometrium. Its further growth is in the direction of least resistance, usually toward the upper and posterior portion of the cornu. Waegli[7] claims that every case of interstitial pregnancy should be regarded as intramural.

Various authors have attempted to classify the types of interstitial pregnancy with appropriate anatomical terminology according to the position in which the ovum becomes fixed in the intramural portion of the tube. Rivlin[20] states that true interstitial pregnancy results only when the ovum becomes fixed in the middle of this portion of the tube. He classified those cases in which the ovum becomes attached nearer the uterine opening and in the process of development grows into the uterine cavity as tubouterine.

Scott's[21] classification is based on the sites of implantation and is the one generally accepted:

1. External, when the ovum occupies the outer third.
2. Middle, when the ovum occupies the middle third.
3. Internal, when the ovum occupies the inner third.

According to this classification the majority of reported cases fall into the first group.

Another division, ascribed to Klebs, is based on the location of embedding, as in the following:

1. Uterointerstitial, when the ovum is embedded in the inner third.
2. Tubointerstitial, when the ovum is embedded in the outer third.
3. Interstitial proper, when the ovum is embedded in the middle third.

The termination of interstitial pregnancy is influenced largely by the location of the site at which the ovum becomes embedded. In the tubointerstitial type, rupture is usually the end result, although incomplete tubal abortion may occur. Webster,[22] in discussing interstitial pregnancy, mentions the possibility of the growing ovum extending into the uterus, developing partly in the tube and partly within the uterine cavity. He has observed a communication between the uterus and fetal sac, closed by a wall formed by the decidua. In still another group, the communication was patent and closed off only by the fetal membranes. Schumann[23] observed three similar instances illustrating these terminations. In the uterointerstitial type, the ovum may completely abort into the uterine cavity.

Some controversial questions arise at this point with the usual differences of opinion. How long does the ovum remain in the intramural portion of the tube? When does it escape into the muscular interspaces? Waegli raises the question as to whether an interstitial pregnancy ever develops solely within the lumen of the tube or only in the muscular wall of the cornu. Conditions present determine when the ovum will escape from the tube proper. It becomes intramural when the lumen of the tube, distended to its anatomical limit, ruptures, allowing the contents to escape and be disseminated into the cornual musculature. We have no way of foretelling when this will happen, but the site of implantation apparently is a deciding factor.

According to Schumann[23] there are three so-called eventualities, preliminary to the escape of the ovum by tubal rupture:

1. The ovum may abort into the uterine cavity and be aborted secondarily from the uterus.
2. The ovum may abort into the uterine cavity and in rare instances continue to grow, with the placenta still attached to the cornu.
3. It may rupture into the uterus, the abdomen, or the broad ligament. In this circumstance the fetus usually dies and a cornual mole may develop.

Curtis[24] and others consider that an interstitial pregnancy tends to rupture about four weeks later than one involving some other portion of the tube. However, Waegli in his publication of 1915 found that, of 38 collated cases, 4 ruptured during the first month, 11 during the second month, 9 during the third, 7 during the fourth, and 7 during the fifth month.

It is claimed that the age at which rupture occurs depends entirely upon the site at which the ovum emplants. If this is at either end of the interstitial portion, rupture will be early. If in the central part, rupture will be late, owing to the protective influence of the thick muscle which surrounds the tube.

We know little or nothing as to how and why the ovum becomes arrested in its passage and the subsequent site and method of implantation. Hennig[25] suggested that the mouth of the tube may be sealed over by an excessive decidual growth, thus preventing the entrance of the ovum into the uterine cavity. When an interstitial pregnancy occurs subsequent to a salpingectomy, the ovum becomes arrested because its progress is blocked mechanically. Its further development follows the same course as in other types of ectopic pregnancies.

The etiology is practically that of an ectopic pregnancy generally, inflammatory lesions of the tube in its interstitial portion being probably the most common cause. Other causes are pathological or abnormal conditions of the tube, among the more important being: (1) congenital, such as exaggerated convolutions, diverticula, kinks, and atresia; (2) sagging and attachments by adhesions; (3) pressure from surrounding growths or structures; (4) thickening of tubal walls, interfering with peristalsis; and (5) destruction of the cilia or narrowing of the tube following salpingitis.

The diagnosis of interstitial pregnancy before rupture is difficult and usually impossible. It depends upon the signs and symptoms associated generally with ectopic pregnancy. Laboratory tests are supplementary. The detection on vaginal examination of an irregular enlargement, firm to the touch, extending around one uterine horn, is suggestive of this condition. The tube and ovary, however, may be normal. Often this enlargement may be intermittent, escaping detection on vaginal examination. This is due to the fact that the muscle fibers at this point, being distensible, retain the normal smooth contour of the fundus. As pointed out by Ballantyne and Murray, this muscular envelope allows the embryo to attain considerable size before the uterus ruptures. Due to the large vessels in the musculature, a rapidly fatal hemorrhage may result.

Intermittent cramplike pain, agonizing in character, limited to the lower abdomen and localized in one or both quadrants, is a characteristic symptom of interstitial pregnancy. It is the main reason above all others for the patient to seek medical relief. Vaginal bleeding may or may not occur.

After rupture, the signs and symptoms are usually the same as those following tubal rupture generally, but more severe. No one can predict what the outcome will be; it is a surgical tragedy. Quoting Parry, "the history of human injury and disease presents no condition parallel to this one." Ash has expressed the opinion that more cases would be recognized and diagnosed before rupture. despite the difficulty of diagnosis, if both the clinicians and specialists would follow the suggestion of Braddock and Scott, "keep in mind the possibility of an interstitial pregnancy when examining any woman at the childbearing age with any deviation from the normal menstrual cycle."

Surgery is the only method of treatment and no delay should be tolerated once the diagnosis has been made, or the condition suspected to be present. The type of operative procedure selected depends on conditions present in the respective patient, especially when extreme speed is necessary to save life, subsequent to rupture.

Bello and associates,[26] to prevent the possible occurrence of interstitial pregnancy subsequent to a previous salpingectomy, advocated total resection of the tube, including the interstitial portion, instead of the usual extrauterine resection. D'Errico quotes Guibe's opinion that this would complicate an operation that should remain a simple procedure.

Kelly[27] in performing a laparotomy found an interstitial pregnancy. He curetted the contents from below. Hirst[28] and Farrar[29] performed similar operations, although Kelly did not advocate this type of procedure. Cornual excision is more speedy, with less danger of serious hemorrhage and infection.

Some surgeons advise hysterectomy in every case, but this appears to be far too radical. If the sac is not too large, the cornu may be excised and the wound closed. This appears to be the operation of choice, if the patient is seen early and is in good physical condition.

At times it might be possible to incise the uterus close to the uterine insertion of the tube and into the tumor mass. After the tumor cavity is entered the products of conception may be removed and the wound then closed with interrupted sutures to control further hemorrhage.

Total or subtotal hysterectomy is indicated is cases seen late, or where this type of operation is technically easier. It can be performed with more speed than extensive cornual resection in patients whose condition is poor, due to shock, hemorrhage, or both. However, if rupture has occurred, a subtotal hysterectomy is the indicated operation, as the element of time is an important factor in prognosis.

Conclusions

1. A case is reported of unruptured interstitial pregnancy, diagnosed before operation.

2. Diagnosis is very difficult due to the distensibility of the uterus at the cornu.

3. Pains are laborlike and intermittent.

4. On examination, irregularity of the uterus is best determined during an attack or immediately after.

5. The use of uterine massage or a minimum of Pituitrin or Ergotrate to produce contraction is advocated as a diagnostic aid.

6. Vaginal bleeding is not significant.

7. In selected cases, incision of the uterine cornu with removal of the products of conception is advocated rather than excision.

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Discussion

DR. GERALD W. GUSTAFSON, Indianapolis, Ind.—This century has seen marked progress in the recognition and treatment of ectopic pregnancy. For instance, Schumann states in his classic monograph on this subject that, in 1882, two of America's foremost gynecologists, in a paper read before the American Gynecological Society, strongly advocated the use of electricity in cases of extrauterine pregnancy. The principle was to destroy the life of the ovum by a strong galvanic current applied to the enlarged tube via the vagina. Both essayists deprecated operative interference until viability of the child when cesarean section was permissible. In the discussion that followed, the opinions generally were in accord with the paper.

Five years later, our American Association was founded and today one of its Fellows has just reported a very remarkable diagnosis of unruptured interstitial pregnancy proved at operation. The preoperative diagnosis was made possible by first being ectopic conscious; second, by proper evaluation of the symptom of intermittent cramplike pains starting approximately ten days after implantation, an earlier period than in the ordinary ectopic pregnancy; and, third, by finding during uterine contractions an irregular mass in the cornu of an enlarged soft uterus without evidence of fibroids or developmental anomalies in a patient who had missed two menstrual periods. The fact that even with the abdomen open the mass was apparent only with uterine contractions is indicative of the brilliance of this diagnosis. The advantages of diagnosis before rupture are obvious. There is little blood loss and the patient can be left with reproductive ability, as pointed out by Dr. Hyams. When rupture occurs, immediate operation with blood replacement is necessary if the patient is to survive.

In going over the records at Indiana University Medical Center, I could find no case reports of interstitial pregnancy in the last ten years, while in the same time there were but

two at the Indianapolis General Hospital. Both patients were young Negro girls, aged 22 and 19 years. Each entered the hospital in shock with abdominal distention and vomiting. One had lower abdominal pain and the other pain in the epigastrium. Both were in about the third month of gestation. One had two children and the other was a primigravida, having had a right salpingo-oophorectomy five months previously. Here the rent in the cornu was beneath the stump of the right tube. Both recovered after subtotal hysterectomy and blood replacement.

The essayist has referred to termination of interstitial pregnancy being influenced by the site of implantation of the ovum. Rupture may occur if the ovum is embedded in any part of the interstitial portion of the tube and is the usual termination if implantation is in the middle third. Here abortion into the uterus may occur, as may also formation of a mole following death of the ovum. In the lower third or uterointerstitial portion, the ovum may abort into the uterine cavity or, rarely, may grow into it and develop to maturity. When the ovum is implanted in the tubal end of the cornual canal, rupture or incomplete tubal abortion may occur. However, if implantation is at the junction of the tube and the interstitial portion, I believe it is possible for the ovum to continue growing upward into the tube, taking the route of lesser resistance, similar to the mechanism of tubal abortion at the fimbriated end of the tube, as shown by Litzenberg. If this be true, then we can have any of the terminations common to tubal pregnancy. In the very rare instance, it should be possible for a tubal interstitial pregnancy to continue growth toward the tube and even a full-term tubal pregnancy occur.

In the latter part of June of this year, I encountered a tubal pregnancy at term, which will be completely reported in the future, similar to the one recently reported by O'Connell. However, in our case, instead of tubal attachment to the uterus, there was an elongated bridge of smooth muscle extending from the right cornu to the sac, suggesting an original tubal interstitial pregnancy.

DR. DAVID B. LUDWIG, Pittsburgh, Pa.—A collection of several series of ectopic pregnancies reveals a reported incidence of 1.16 per cent of the interstitial type. Our personal experience of ectopic pregnancies extends over a period of thirty-one years and is comprised of 330 cases. Four of these, or 1.21 per cent, were interstitial pregnancies.

In the first of these cases, the pregnancy was early, had not ruptured, and was removed very easily. The pregnancy mass was located in the outer third of the interstitial portion of the tube, and might be classified a tubointerstitial pregnancy.

The second case offered some difficulty in diagnosis. An otherwise clear picture of ectopic pregnancy was beclouded by a marked elevation of temperature and history of attempted abortion. Pelvic examination revealed a soft, very tender mass on the right side which was considered to be outside the uterus, and laparotomy was performed. An interstitial pregnancy was encountered which required resection of a considerable portion of the right side of the uterus.

The usual picture of ruptured ectopic pregnancy with extensive intraabdominal hemorrhage was presented in the next case. The radial pulse was perceptible only at times, the apical heart rate being 120 per minute. The blood pressure was 55 systolic and 35 diastolic. The patient had had a right salpingectomy ten and one-half months earlier for a ruptured tubal pregnancy, a modified Coffey suspension of the uterus being performed on the right side at that time to effect peritonization.

Vaginal examination was deferred owing to the condition of the patient and diagnosis was made of left tubal pregnancy with rupture. Upon commencement of blood transfusion, a left lower abdominal incision was made. The left tube and ovary were found to be normal; however, the pathology consisted of an interstitial pregnancy of the right side. In an attempt to resect a portion of the soft friable uterus, bleeding could not be controlled and a hysterectomy and right oophorectomy were necessary.

Our last patient had been bleeding rather profusely from the vagina for three days when first seen and presented a red blood count of 2 million and a hemoglobin of 5½ Gm. Vaginal examination was not made. Operation was performed shortly after admission upon

commencement of blood transfusion. An ectopic mass including almost half of the right side of the fundus was resected. This patient has become pregnant on two subsequent occasions, two and six years later, being delivered successfully in both instances by cesarean section. The uterus at the time of the second section was observed to be quite uniform in outline.

All patients convalesced uneventfully.

DR. C. DENTON KERR, Houston, Texas.—Since interstitial pregnancy was first described by Schmitt in 1801 it has remained among the most serious emergencies that confront the obstetrician and gynecologist. It occurs so rarely no individual has the opportunity or the misfortune of seeing any appreciable number of patients suffering from this condition. The seriousness and the infrequency of interstitial pregnancy combine to make an occasional presentation such as we have heard today very necessary. When one begins reviewing the histories, the description of the operative findings and procedures, as well as the gross and microscopic reports of different clinicians and pathologists, one is still more reminded of the need for more intensive study of this entity.

In one case of so-called cornual pregnancy which I reviewed, the operator said: "The right cornu of the uterus was enlarged by a spongy, hemorrhagic mass, measuring about 6 by 8 cm." No reference to the tube on that side was made. The operator's pre- and postoperative diagnosis was "ruptured tubal pregnancy." In describing the gross specimen the pathologist said: "This hemorrhagic mass distends cornu into the tube and is a cornual pregnancy." Under the microscopic description of the same specimen the following statement is made: "The right tube contains clotted blood and necrotic material. The latter includes chorionic villi. The wall consists of enlarged muscle fibers." The pathologist's diagnosis is, "Tubal pregnancy, right." Obviously neither the surgeon nor the pathologist was particularly concerned about the exact diagnosis. The same lack of interest and cooperation was evident throughout the entire study of 21 cases with a final discharge diagnosis of interstitial pregnancy. A thorough study revealed only 3 that could be called true interstitial and 8 that could be called tubointerstitial pregnancies. The remaining 10 cases were either obviously tubal pregnancies or there was insufficient evidence to classify them and therefore they had to be discarded.

In reviewing 74,403 deliveries in four hospitals in Houston, Texas, over a five-year period I found 403 ectopic pregnancies. Of these, 3 were true interstitial while 8 were of the tubointerstitial type. None of these were correctly diagnosed before rupture. Only 2 cases were suspected of being interstitial in type before the abdomen was opened.

It is reported that from 0.5 per cent to 1.3 per cent of all pregnancies are outside the uterine cavity. A further breakdown of this abnormal type of pregnancy indicates that somewhere between 0.65 per cent and 2 per cent of the ectopic pregnancies are interstitial. Using these extremes, the 74,000 pregnancies should have resulted in from 372 to 967 ectopic pregnancies, with from 2 to 19 of these being of the interstitial variety. This wide variation in figures is significant. It means either that the series reported are too small to be conclusive or that the knowledge of and interest in this dangerous condition are lacking.

DR. EMIL NOVAK, Baltimore, Md.—A well-known gynecologist of the preceding generation used to say that the man most likely to diagnose tubal pregnancy was the one who always had it "on the brain." The only trouble with such an aphorism is that such a man would be quite sure to diagnose many tubal pregnancies that "ain't." There are only one or two points in Dr. Hyam's paper on which I should like to comment.

In his case you will note that, although his patient was 2½ months pregnant, there had been, as I recall it, only one tiny episode of vaginal staining. This illustrates what I believe to be a general principle with tubal pregnancy, that so long as the pregnancy is a going concern, and the embryo somatically alive, it mothers and protects the decidua, and external bleeding does not occur. With the death of the embryo, the decidua regresses and is cast off, with external bleeding as the result. Many years ago Darner and I studied a large series of tubal pregnancies in the collection of the Carnegie Institute of Embryology and found this general rule to hold good.

As regards intra-abdominal bleeding with interstitial pregnancy, Dr. Hyams has already mentioned that rupture takes place later than with the far more common ampullary or

fimbriated end varieties. However, when rupture does take place, it may occur with a bang, and with profuse bleeding which may be catastrophic and even fatal. My first case of interstitial pregnancy, and one of the first of any kind of ectopic gestation, was seen when I was a young intern. A Negro woman was brought in dying, and she did die, of a cataclysmic abdominal hemorrhage from a ruptured interstitial pregnancy, the whole cornual region being literally blasted away. Incidentally, she had had no vaginal bleeding.

DR. RALPH A. REIS, Chicago, Ill.—Most of us, at some time or other, have opened an abdomen for a suspected interstitial pregnancy, and in the majority of instances have found simply an exaggerated Piskacek sign. I wonder, then, whether the admonition to inject Pituitrin or Ergotrate to make the uterus contract, when in doubt, will not result in the dislodging of many more normally implanted fetuses than it will assist in the diagnosis of this very rare condition. A simpler and safer way is to massage the corpus gently and to observe the resultant contraction.

DR. JAMES E. DAVIS(Dexter, Mich.—In the first volume of the Transactions of this Association, 48 pages are devoted to discussions of extrauterine pregnancy.

The distinguished discussants included Joseph Price, E. E. Montgomery, J. M. Baldy, John M. Deaver, L. S. McMurtry, F. Townsend, W. H. Wathen, H. T. Byford, and A. Vanderveer. In this symposium, Dr. Baldy facetiously commented that a positive diagnosis of a high percentage of these ectopic pregnancies was beyond the reach of man. After the passing of 64 years some present-day diagnosticians hold the same opinion.

Advances have, however, been made. The pregnancy blood test using the African female toad (*Xenopus laevis*) or the rabbit is a biological diagnostic aid of signal value. Better appreciation of tubal pathology and of endometrial tissue displacements extends the certainty of correct diagnostic evaluations. Microscopic sections well selected from the tubomyometrial area offer good stimulation for exacting diagnostic possibilites.

Traces of implantations at any elapsed period of time are well illustrated in the case of Mrs. Canty at the age of 77 years, whose tissue encased a cyst wall for 50 years which surrounded a perfect lithopedion weighing 8 pounds. Microscopic sections indicated the causative factor to have been endometrium displaced into the proximal end of the oviduct.

The term ''interstitial'' should be discarded. Anatomic location is satisfactorily described by the term myo-oviductal. The word interstitial is unsuitable because it refers the mind to interspaces. The pathology of interspaces is of little value and leads in a very limited way to the needed or completed structural changes from the normal.

DR. HYAMS (Closing).—In answer to Dr. Reis, I am very happy he brought up the subject of the use of Pituitrin or Ergotrate as a diagnostic aid. Unfortunately, the preoperative diagnosis of unruptured cornual pregnancy is very difficult and, on account of its rarity, is frequently not thought of, in interpretating the symptoms. When this condition is encountered while the abdomen is open, the diagnosis is often evident and appropriate surgery can be instituted. However sometimes the uterus might be completely relaxed and nothing found to account for the preoperative symptoms. It would be unfortunate to terminate the operative procedure without ruling out in some way the presence or absence of an interstitial pregnancy. In such an instance, massage of the uterus or the administration of Pituitrin or Ergotrate in minimum quantities sufficient to produce contraction of the uterus and evidence of cornual enlargement is of great advantage. Subsequent recurrence of symptoms and even rupture of the uterus can thus be prevented. Fortunately, in the case reported, massage of the uterus was all that was necessary to produce uterine contraction and the evidence of an abnormal growth. The promiscuous use of Ergotrate or Pituitrin has its disadvantages and they must be used with caution. One who has been associated with the late Dr. John Polak can never forget the ever-present possibility of extrauterine pregnancy.

Some feel that in performing salpingectomy, the cornu of the uterus should be excised completely in order to prevent the possibility of a cornual pregnancy occuring later. Returning to our own case report, three months after operation a uterosalpingogram was done. Nothing could be found in the x-rays to account for the previous abnormal pregnancy.

A COMPARISON OF THE LOW CERVICAL AND CLASSICAL CESAREAN SECTION OPERATIONS*

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THERE is considerable difference of opinion regarding the relative merits of the classical and low cervical cesarean sections among experienced obstetricians in this and other countries. The difficulty in evaluating the results of a given operation, as opposed to those obtained by the same operation done by a different technique, lies in the fact that the men who report series of cases have for the most part each adopted one or the other procedure as best suited to his needs and experience and performed the operation of his choice to the exclusion of other methods. Furthermore, an operator working with material such as comes to Cook County Hospital or Bellevue cannot justly be expected to show as good results from his efforts as would the same man working with the facilities of the Chicago, New York, or Philadelphia Lying-In Hospital.

Previous to 1900 the classical operation was done almost exclusively. With the turn of the century the Krönig[1] operation was popularized. This is the one most frequently done in the United States at this time, although modified in minor details by some surgeons. DeLee[2] became very enthusiastic regarding its advantages and preached and practiced the operation so successfully that he converted most of the western and midwestern specialists to its use. J. W. Williams[3] was never convinced that the classical operation was inferior to the low cervical except in cases that were potentially infected, in which he agreed that possibly the infection, if it did penetrate the uterine wall, would be less dangerous behind the bladder flap than emptying into the peritoneal cavity direct. Schumann[4] thinks that in clean cases the classical operation is very satisfactory and reserves the low cervical for cases with long ruptured membranes, slight temperature, or patients who have had vaginal examinations with questionable technique. Eastman[5] prefers the classical for clean cases not in labor more than six hours and the low cervical for potentially infected ones and either extraperitoneal or the Porro for those frankly infected. Titus[6] felt that the arguments advanced for the use of the low cervical by DeLee and others were valid and had given up doing the classical operation for those reasons. J. Clarence Webster,[7] as early as 1910, had done 400 cases by the classical technique and without mortality. Greenhill[8] believes that the laparotrachelotomy should replace the old classical cesarean section in all but special cases and cites the following advantages: The spill of amniotic fluid is limited to the lowest portion of the abdomen, the hemorrhage is less and more easily controlled since it is in full view. The omentum and intestines do not come into view and there is less peritoneal shock. The operation is technically more difficult but such skill should be

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possessed by a physician who considers himself capable of doing an abdominal delivery. He feels that postoperative complications such as ileus, gastric dilatation, and peritonitis are conspicuously absent. This is due to better control of the amniotic fluid spill, the decreased exposure and manipulation of the peritoneum, intestines, and omentum; and because the uterine closure is in the lower uterine segment, accurately coapted, at rest during the healing process, and thickly covered by fascia and peritoneum, which almost completely prevents seepage of lochia. D'Esopo[9] reports 487 cases by low cervical cesarean section, and 456 by classical cesarean section done at Sloane Hospital. The classical operation, because of fewer steps, he feels is the quicker and easier to perform and thus, in cases in which speed is important, because of the gravity of either the maternal or fetal condition, this operation may be favored. Also, since the comparison of the immediate end results of the classical and low flap operations done in elective cases shows no significant differences, the choice here becomes equivocal and may then lie with the easier classical technique. In their series there appeared to be 50 c.c. less blood loss in the low flap operations as compared with the classical procedure.

From a consideration of these views I was convinced that the maternal salvage attributed to laparotrachelotomy by some surgeons was due to a number of circumstances which were difficult to evaluate because of the divergent training and experience of the operators who were contrasting the results in series of cases done by one of these techniques.

Because I was not convinced by the claims of various authorities that the low cervical cesarean section was a better or safer operation than the classical operation when both were undertaken in patients not grossly infected, I started an experiment which has taken 26 years to complete. In brief, the task was to operate upon a series of patients, alternating between the two operations without respect to the indications or conditions of either the mothers or babies. When 100 cases were done in this manner a preliminary report was made before this society. The results were so similar in the two series that it was decided that more operations would have to be done to make the figures statistically significant. I now report 500 operations done as before in the same rooms, by the same operator, on the same type of patient, and with the same type of assistants, both medical and nursing personnel. From time to time there was some change in the type of anesthetic, personnel administering the anesthetic, and anesthetizing procedures but these involved both groups of patients equally and therefore could not have affected the outcome of the operations appreciably.

As in the first series, it was thought necessary to make certain observations to ensure the fact that complications inherent in the case itself would not influence the result of the operation. For this reason a careful compilation of all important complications was made in each case and proper weight accorded to each in the final analysis of the case for comparison.

Certain criteria were set up to judge the superiority of one or the other operation, such as the difficulty of the operation as shown by the elapsed operative time, the postoperative stay in the hospital, and the amount of sedative used to keep the patient comfortable after the operation. Since the bladder is moved downward to expose the lower uterine segment in the laparotrachelotomy, it was thought that dysfunction might result from such trauma

and so catheterization might be more frequently necessitated. It is frequently stated as a criticism of the classical procedure that the amniotic fluid spill into the abdomen results in much more irritation, more severe gas pains, and considerable paralytic ileus with nausea and vomiting. We gauged this by comparing the numbers of enemas that were necessary for relief of distention and discomfort as well as the before-mentioned sedatives. Postoperative complications such as wound infections, pneumonia, thrombosis, emboli, and dehiscence were recorded when present.

The outcome of the operation for the baby as well as for the mother was considered, a factor not sufficiently stressed in many discussions on cesarean section. In some of the fatal cases, as shown by the case history, the operation was undertaken solely in the interest of the baby since the outcome for the mother was hopeless at the time the decision to operate had to be made. Such decisions necessarily help to spoil statistics as far as maternal mortality is concerned and as a matter of fact do not improve the fetal mortality statistics as much as one would like to see. However, when the case is finally evaluated and the summary made, it gives you a good feeling to know that in your best judgment both patients were given the best chance for survival that the conditions surrounding the case permitted. It is therefore necessary that we compare the two operations in their relation to the fetus as well as to the mother.

In order that there may be a clear understanding regarding our concept of a low cervical and a classical cesarean section, I will say that by definition the former is a hysterotomy in which all or nearly all of the incision is made between the cervix and the upper or contractile portion of the uterus. The classical operation places the incision in the upper uterine segment almost completely, possibly about one tenth of the incision extending downward into the lower uterine segment. I am aware that many men claim to stay within the lower uterine segment entirely when doing the low cervical operation, and I am also aware of the fact that it cannot be done except in the abnormal cases in which the lower uterine segment is elongated by the formation of a rising Bandl's ring. A brief description of the technique employed in the two groups is presented:

Low Cervical Cesarean Section

1. The patient is placed in the Trendelenburg position. A midline incision from the symphysis to near the umbilicus is made as soon as the anesthetist has the patient relaxed.
2. A transverse incision is made in the uterovesical fold at its uterine attachment.
3. The peritoneum and bladder are freed from the lower uterine segment and displaced downward.
4. A lap pad is placed above the line of incision to catch the spill not aspirated by the suction apparatus.
5. Injection of 1 c.c. of obstetrical Pituitrin is made into the uterine muscle immediately before making the incision.
6. A longitudinal incision 12 to 14 cm. long is made in the lower uterine segment extending upward from the cervix. The baby is delivered by forceps or by fundal pressure in a few cases.

7. The wound edges are seized by Allis forceps at bleeding points and the placenta which by this time is separated as a rule from the uterine wall is gently extracted and all membranes are peeled off the interior of the uterus.

8. The wound edges are sewed by two layers of continuous catgut sutures, after which the peritoneum of the uterovesical fold is brought back to its original position by a continuous fine plain catgut suture, thus covering the longitudinal incision in the lower uterine segment.

9. The abdomen is closed in layers and two tension sutures and skin clips are used.

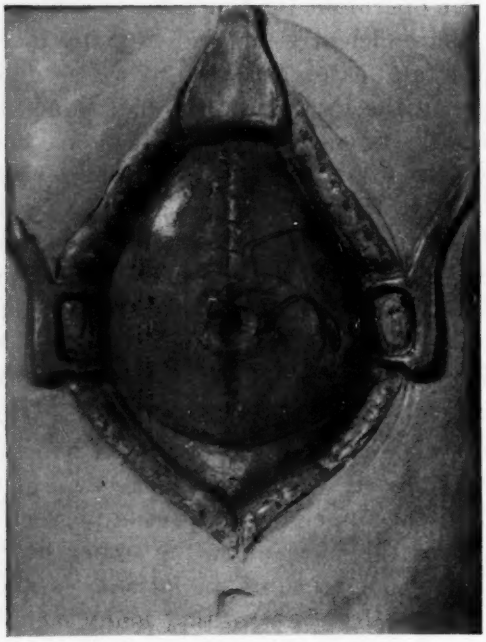

Fig. 1.—The lower uterine segment was incised longitudinally and closed by two running sutures.

Classical Cesarean Section

The classical section is also carried out through a subumbilical midline incision, with the upper abdomen partially packed off with a lap pad. The uterine incision is begun about 2 inches above the level of the umbilicus and continued downward 12 to 14 cm. Pituitary extract, 1 c.c., is injected into the uterine muscle in most cases just before the incision is made and the uterus thus starts contracting in response at the beginning of the third stage.

The baby is delivered by breech extraction followed immediately by manual removal of the placenta. The uterine wall is closed by three running sutures, the first including the uterine musculature of about one-half of the thickness of the wall and extending to the mucosa. The second layer from under the serosa interdigitates with the first layer and emerges under the serosa of the opposite side. The third suture passes through the serosa and outer musculature and interdigitates with the second layer. The peritoneum is then united with a fine plain running suture which covers the previous suture line (not shown in illustration).

Sterilization is carried out in some cases by excision of the cornual portion of the tubes after they are tied off distally and closing the defect in the cornua over the uterine end of the interstitial portion of the tube.

All patients were kept in bed about ten days and sent home on the twelfth day unless there was some obvious complication or they lived at some distance from Chicago.

Mortality

There is a tendency among surgeons to evaluate an operation on the basis of mortality which results in some of the postoperative cases. This in many respects is quite illogical and unfair to the operation. Only after a critical survey of the facts surrounding the death can one attribute to the operative procedure a major, minor, or nonsignificant role in the ultimate outcome.

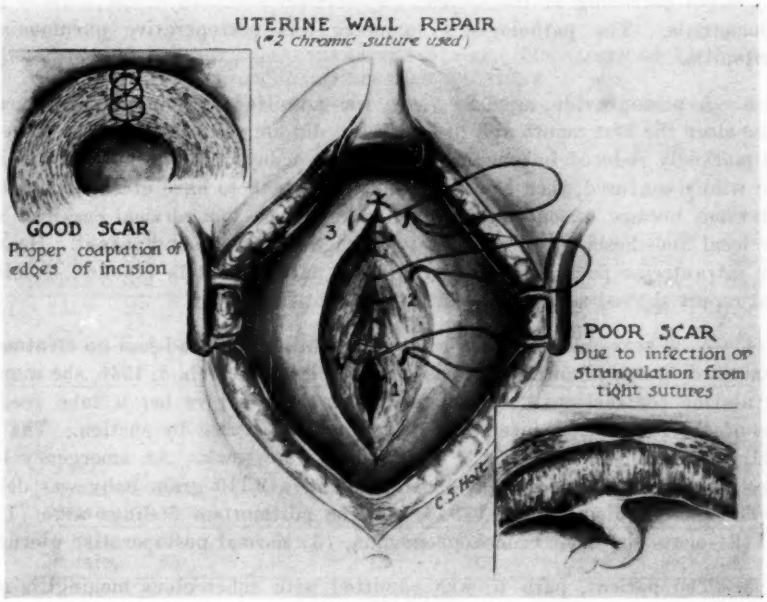

Fig. 2.—The technique of closure of the classical cesarean section in three layers is shown. The potential danger of rupture during subsequent pregnancy is indicated in the right lower insert.

Case 1.—A para i, aged 40 years, was admitted February 2, with a diagnosis of preeclamptic toxemia, blood pressure 190/115, albumin 1 plus, and marked edema. She improved slightly under medical management until February 19, when she had epigastric pain and vomiting. Because of the prematurity of the fetus she was carried along under medical management for 9 days when, because of fetal heart tones varying from 86 to 162, a classical cesarean section was performed on February 28. She was not in labor, the temperature was 98.8° F., pulse 98, respirations 20. No difficulties were encountered at operation. The operation lasted 47 minutes under local anesthesia and she was sterilized. The temperature varied from 101° to 101.8° F. on each of the four postoperative days. Her condition was fair on the second day; on the third day she developed a chill and cough and physical findings of pneumonia with 3 plus albumin and she died on the fourth day. A postmortem examination revealed: (1) normal postmortem uterus; (2) extreme fatty degeneration of the liver; (3) bronchopneumonia of right upper lobe; (4) marked pulmonary congestion; (5) recent ulcerative colitis; (6) marked bowel distention; (7) arteriosclerosis of the kidney with marked fatty degeneration and general arteriosclerosis. The cause of death was postoperative pneumonia superimposed on the degenerative changes in the liver and kidney secondary to severe eclamptogenic toxemia.

Case 2.—A Negro syphilitic woman, para 0, aged 37 years, was first seen in the outpatient clinic December 24. She was admitted to the ward December 26 in early labor, with weak pains and polyhydramnios. She had an android pelvis with contracted outlet. Mem-

branes were ruptured, there was 2 cm. cervical dilatation, and the head was at minus 3 station. On December 27 at 10 A.M., there was no progress, fetal heart tones were 160, albumin 2 plus, blood pressure 140/100. A classical cesarean section was done in 43 minutes. An arcuate type of bicornuate uterus was found. The baby weighed 3,640 grams, was in good condition, and survived. On the first postoperative day the patient had a temperature of 103.8° F., and on the third day a temperature of 104.6° and the impression from physical examination was bronchopneumonia. She died on the fourth postoperative day and the postmortem revealed (1) fibropurulent peritonitis (pneumococci); (2) retained small piece placentral tissue; (3) bilateral edema and hyperemia of the lungs; (4) bilateral fibrinous and interlobar pleuritis; (5) syphilitic aortitis; (6) arteriosclerosis of the aorta and left coronary artery; (7) slight softening of the spleen; (8) cortical adenoma of the adrenal; (9) saprophytic endometritis. The pathologist's summary was postoperative pneumonia with secondary peritonitis.

CASE 3.—A primigravida, aged 24 years, was admitted without prenatal care. She had had jaundice since the first month and ill health but did not see a doctor. The urine was bright yellow and markedly reduced in amount for the past 4 days and the patient was incontinent. She became wildly confused, then comatose, and then began to have uterine contractions. The fetal heart tones became uncountable and an antemortem low cervical cesarean section was done under local anesthesia in an attempt to salvage the 3½ pound infant. Heavy bleeding required an intrauterine pack at operation and the patient died in 7 hours, 45 minutes. The pathological report showed acute yellow atrophy of the liver.

CASE 4.—A 30-year-old primipara who was syphilitic and had had no treatment for this and no prenatal care was admitted in coma Feb. 6, 1946. On Feb. 8, 1946, she went into labor with weak uterine contractions. An attempt was made to give her a tube feeding during which some of the fluid was aspirated and had to be recovered by suction. The fetal heart tones shortly thereafter rose from 120 to 170 and were weak. An emergency low cervical cesarean section was done under local anesthesia and a 2,110 gram baby was delivered who survived. The mother died Feb. 11, 1946, and the postmortem findings were (1) syphilitic meningitis, (2) acute confluent bronchopneumonia, (3) normal postoperative uterus.

CASE 5.—The patient, para ii, was admitted with tuberculous meningitis and miliary tuberculosis. On August 20 she was placed on medical management, and under local anesthesia a 2,350 gram baby was delivered by classical cesarean section. The mother died 57 days later from tuberculosis without evidence of pelvic pathology as shown by autopsy.

CASE 6.—A 28-year-old gravida v, para iii, who was Rh negative and whose husband was Rh positive, was admitted at the twenty-ninth week with a weight gain of 18 pounds in 11 days. She was very obese, weight 175 pounds. Blood pressure was 160/100, albuminuria 4 plus, and phenolsulfonphthalein test was 40 per cent in 2 hours. She did not do well on medical management so after 4 days, in spite of the fetal prematurity, it was decided to do a classical cesarean section. The fetus had not seemed abnormal as judged by heart tones and x-ray. Postmortem findings were (1) uterus showing no evidence of infection; (2) no peritonitis; (3) fatty degeneration of the liver and periportal necrosis; (4) edema of the kidney tubules and bilateral pyelonephritis; (5) softening of the myocardium; (6) hyperemia and edema of the lungs; (7) hyperemia of the spleen.

CASE 7.—A 33-year-old para iv who had had a previous spontaneous delivery was admitted Nov. 13, 1943, with a diagnosis of multiple sclerosis and was moribund. She was not expected to live more than one or two weeks. A classical cesarean section was done on November 20 and she died on November 26. The postmortem examination showed (1) advanced multiple sclerosis with bulbar involvement; (2) bilateral lower lobe atelectasis; (3) aspiration bronchopneumonia of the left lower lobe; (4) fibrosis of the myocardium; (5) chronic passive congestion of the lungs; (6) hemorrhagic cystitis; (7) right hydronephrosis and hydroureter; (8) arteriosclerosis; (9) hemangioma of the liver; (10) postoperative uninfected uterus.

Table I shows a summary of the statistical data compiled during the course of this study. It is seen that the ages of the two groups were exactly the same and that there were a slightly smaller number of Negro patients in the classical group. There were approximately the same number of primiparas in each group, and a slightly greater number of cases of toxemias in the classical group. This may have contributed to the increased mortality in this group since the postmortems showed that 4 of the 7 deaths were due to this cause. Membranes were ruptured in 40 low cervical cases as opposed to the 29 in the classical series. This does not imply that we did the low cervical deliberately in these cases since our object was to accept the condition as a calculated risk and see what we could discover regarding it.

TABLE I. COMPARATIVE STATISTICS, ALTERNATING SERIES. 500 CASES OF LOW CERVICAL AND CLASSICAL CESAREAN SECTIONS

	NO. OF CASES	AVERAGE AGE	RACE		PRIMIPARAS	CASES OF TOXEMIA	RUPT. MEMB. BEFORE C. S.	SPONTANEOUS LABOR FOLLOWING SECTION	REPEAT CES. SECTION	RUPTURED UTERUS
			WHITE	NEGRO						
Low cervical	250	27	49	51	88	69	40	7	50	0
Classical	250	27	58	42	86	76	29	4	55	1

Maternal Considerations

	AVER. OPER. TIME	STERILIZATION	AVER. NO. P.O. DAYS TEMP. ABOVE 100°	P.O. DAYS IN HOSP.	WOUND INFECTION	AVERAGE MORPHINE	AVER. CODEINE	MORE THAN 1 ENEMA USED	TOTAL CATH. POST. OPER.
Low cervical	38 min.	60	1.94	13	22	8/12 gr.	6 gr.	111	262
Classical	38 min.	85	1.97	13	19	10/12 gr.	8 gr.	121	294

Fetal Mortality

	STILLBORN	PREMATURE 1,000-2,500 GRAMS	ABOVE 2,500 GRAMS
Low cervical	6	13	5
Classical	9	14	3

We found on going back into our records that 11 patients had come back for subsequent delivery and that 7 who had had low cervical and 4 who had had classical sections delivered uneventfully. We did repeat cesarean sections on 50 who had had low cervical and 55 who had had classical sections. There was no significant difference noted between the two series as regards adhesions between the uterine and abdominal walls or between loops of bowel. One ruptured uterus occurred in a patient not in labor about 30 weeks pregnant who had had a classical operation.

The claim is made by many advocates of the classical operation that it is easier and quicker to do. We have felt this not to be true as far as the technical difficulties are concerned for one familiar with the low cervical operation. Our average operating time was 38 minutes for both series. About the only factor that could have influenced the comparison is that 25 more sterilizations were done in the classical than in the low cervical group, and I estimate that this adds about five minutes to the operating time. When one considers, however, that it is slightly more awkward to get at the tubes after low cervical operations it would seem that this would offset the additional time consumed in sterilizing an additional number in the classical cases.

A temperature of 100° F. on any postoperative day was used as our criterion of morbidity. By this standard the average for the low cervical operations was 1.99 days. Each group averaged 13 days in the hospital, and there were 22 mild wound infections in the low cervical group as opposed to 19 in the classical group. This includes mild infections of any kind such as might be seen around a catgut knot.

Postoperative pain and paralytic ileus have been stated to be much more marked following classical than low cervical cesarean section and this is due to the increased soiling of the peritoneal cavity by uterine spill at operation. With the use of the suction apparatus we feel that this is not necessarily true if one walls off the general peritoneal cavity by well-placed laparotomy sponges. As a measure of this discomfort we found that an average dose of $^{8}/_{12}$ grain of morphine and 0.6 grain of codeine was used for relief in the low cervical group and $^{10}/_{12}$ morphine and 0.8 codeine in the classical group. We use an enema routinely on the morning of the second postoperative day. In the low cervical group it was necessary to supplement this by 111 enemas while in the classical group 121 were used.

Since in the low cervical section the bladder is displaced downward it has been argued that more postoperative discomfort might be expected in this group from dysuria. Clinically this was found not to be the case and we noted that catheterization was necessary in 262 of the low cervical and 294 in the classical group.

As regards the fetus, it was found that 6 infants in the low cervical series were stillborn as opposed to 9 in the classical. Nothing which occurred during operation appeared to have had any influence in determining these results. The prematures between 1,000 and 2,500 grams in weight showed an equal number of deaths. Five of the babies in the low cervical group died compared with 13 in the classical group, an insignificant difference.

Conclusions

1. Five hundred cases have been studied, a sufficient number to be statistically significant.

2. The conditions surrounding the operations were as nearly identical as we could make them.

3. They were done by one operator unprejudiced in favor of either operation with sufficient experience in each operation before beginning this series to carry out the technique of both with equal facility.

4. The operations are found to be equally difficult, and to produce approximately the same amount of postoperative morbidity, discomfort, and complications.

5. The autopsy showed a normal postoperative uterus in six out of seven deaths.

6. These six cases showed pathology probably incompatible with recovery whatever type of delivery had been used. In the remaining case a saprophytic infection of the uterus was noted but the cause of death was given as postoperative pneumonia and secondary fibropurulent pneumococcic peritonitis.

7. The common causes of death from cesarean section which could be attributed to the operation directly, such as shock, hemorrhage, anesthesia, puerperal infection spreading from the operative site, are not seen in either series.

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Discussion

DR. J. P. GREENHILL, Chicago, Ill.—You know, of course, of the debate many years ago between Dr. Williams and Dr. DeLee about the merits of the cervical cesarean section versus those of the classical operation. Dr. Williams was enormously influenced by the contention of Dr. Halsted, then professor of surgery at Johns Hopkins, that the low cervical operation was unanatomic and unphysiologic. That may have been the sole reason for Williams' aversion to the cervical operation. Falls, as was I, was trained by Dr. DeLee but he departed from some of Dr. DeLee's teaching. Perhaps that is the reason he decided to run this series of cases and continue for 27 years. I stuck to my original teaching and kept on and I have been quoted twice today as being a strong advocate of the cervical cesarean section, which I most assuredly am.

Many years ago I reviewed all the cesarean sections done at the old Chicago Lying-in Hospital. I found that in the hands of the same operators in this institution the death rate for the classical operation was about three times as high as for the cervical. Falls maintains that the death rate should not be used as the sole criterion of the safety of the two operations. This criterion was very important up to a few years ago but it is less significant today. In spite of this I still feel that the cervical cesarean section has definite advantages over the classic operation; namely, better peritonization of the wound, which I consider very advantageous, and, second, a distinct decrease in the frequency of rupture of the uterus in subsequent pregnancies and labors. Falls showed on the screen that there was one rupture of the uterus among the four patients who had classical cesarean sections. Of course this small number means nothing, but statistically throughout the world there is a tremendous disproportion between the frequency of rupture of the uterus not only in labor but also in pregnancy following the classical operation as compared with the cervical. Now what does all our talking add up to? I think that in spite of all the discussion that has gone on and will go on, each of us will continue to do the cervical or the classical cesarean section as we have been trained to do, because the immediate results of both are almost identical at the present time. Nevertheless, the cervical operation has the advantages of peritonization and far fewer ruptures, and these are very significant advantages.

DR. C. MAC INTOSH MARSHALL, Liverpool, England.—I have done nothing but cervical cesarean sections for the last 17 years. Occasionally that operation has become a hysterectomy but never on account of the risk of infection. In that series of cases there has been a considerable percentage of women who have been in labor 48 hours or more and also a considerable percentage who had had previous attempts at delivery. Many of these patients were operated upon before both the sulfanilamide and the penicillin era.

Recently in a paper published in the American Journal of Obstetrics and Gynecology, Dr. Falls paid me the compliment of referring to that first series which I published in 1939 of 250 cases; the first 250 cesarean sections I had ever done without any mortality

whatever. He pointed out that these operations were all done before we had this umbrella to protect us from infection. We have not lost a woman from infection in the Liverpool Maternity Hospital in the last twelve years, and we have in all cases conserved the uterus. In other words, we do not believe in our practice that Porro cesarean section is necessary. Admittedly, since 1941, I have done an occasional extraperitoneal section, but in all a comparatively small number. Statistics do not always show the truth, even supposing that there is no immediate difference between the classical and lower segment types of operation.

I believe there are the following differences which I have seen clinically and at operation: (1) The risk of postoperative adhesions is greatly reduced if the incision is placed in the lower segment and the incision covered by the uterovesical peritoneum. (2) The risk of rupture in the future of that lower segment scar, if it has been a transverse scar and confined to the lower segment, is definitely less than of the classical incision. There is only one technical difficulty in the low segment operation. In the hands of the beginner, extraction of the head especially after a long labor may be difficult. Patience and deliberation are all that is necessary. The problem is to get that head which has partially entered the brim out of the pelvis, but even supposing it takes us five minutes, the child is still in contact with an undisturbed placental site. The manipulations required are actually no more violent, no more lengthy than those required in a vaginal delivery with, let us say, a manual rotation, or the application of Kielland's forceps. The reason that people occasionally lose babies, as I have observed, is because they feel they must hurry. The third stage of labor is really the only stage that the expert obstetrician has to worry over, and that third stage at cesarean section can be made absolutely safe by giving intravenous ergometrine at the moment the small obstetric forceps is applied to the head and one is drawing it slowly through the uterine incision.

DR. HAROLD HENDERSON, Detroit Michigan.—Many of us have lived through the era when, under the influence of Krönig, Alfred Beck, and J. B. DeLee, the trend was away from the easier classical technique to the more difficult low cervical operation. Dr. Falls lists the reasons why the latter operation was, and still is, considered by most obstetricians the acceptable procedure. He then proves in a most careful and unprejudiced analysis of a series of cases significantly large, that there is practically no difference in the results of the two operations. This would be a shock to us who call ourselves modern obstetricians had we not already been aware of his interest in this problem and the impartial study that he has been making.

In Detroit, as in most medical centers, the tendency is to emphasize the low cervical operation. For example, of 312 recent sections done in Herman Kiefer, Harper, and Providence Hospitals, 285 were low cervical, 18 were classical, 8 were cesarean hysterectomies, and one an extraperitoneal section. In 1925, Welz reported that of 154 sections done in Detroit only 11 were low cervical with a mortality of 3.3 per cent in the classical and 9 per cent in the low cervical. Seeley, in 1930, repeating Welz's study, reported 208 sections with a mortality of 5 per cent. Eighty-eight of these were of the low cervical type with no deaths.

The trend away from the classical operation was led by obstetricians. The surgeon of the first quarter of the century gloried in the speed of a theatrical delivery. The diversity of his surgical interests left him cold to the slower and more difficult dissection of the Krönig operation. The obstetrician, however, in his zeal for lowered morbidity and mortality, took pains to develop the particular surgical skill demanded by the newer technique. In 1926 DeLee, the most enthusiastic advocate of this method, listed 16 reasons to prove his point. High in his list were decreased morbidity and mortality from infection, a lessened number of adhesions, and a decrease in the number of ruptured uteri. All this happened before the use of sulfonamides and antibiotics and when blood transfusion was used as a heroic effort to save a moribund patient.

We are in another surgical era and it is fitting that we should re-examine our reasons for continuing a practice which we started over a quarter of a century ago. There

is now almost no mortality from the operation itself. There was only one death in our series. This was in a case of abruptio placentae in which a classical section was done. It is not surprising, therefore, that in the hands of an astute and skillful operator there will be little difference in the results of the two procedures. However, in the 1920's, when most of the operative obstetrics fell into the hands of surgeons of varying degrees of skill and when we had no specific treatment for infection and inadequate means for combating hemorrhage, one cannot help but feel that the advantages of the low cervical section were magnified. Now, even if there is an appreciable difference in the amount of hemorrhage and in susceptibility to infection, the statistical results of the two operations should be much more nearly approximated.

This leaves two considerations which must be evaluated to determine our decision as to which type of operation to use. First is the incidence of adhesions and, second, the frequency of rupture of the uterus. From the theoretical standpoint, there should be no comparison between the two procedures in the matter of adhesions. In the classical technique it is difficult to cover the uterine wound with peritoneum. After the closure, there may be small areas of pouching myometrium that are difficult to cover with serosa. In the low cervical operation there is ample loose peritoneum and we can easily invert the edges, thus presenting to the peritoneal cavity no raw surfaces. We found that in repeat sections 26 per cent had adhesions following low cervical section and 43 per cent after classical section. These figures may seem high but they represent the work of a variety of operators.

May I call attention to the fact that our judgment is based not only on statistical analyses such as this but also on clinical experience which is difficult to put into figures. Years ago I was convinced that adhesions were a severe complication of the classical section. That others shared this feeling is pointed up by the fact that a supraumbilical incision was used by some authorities to prevent the uterus from adhering to the abdominal wall. My personal experience in repeat sections has demonstrated to my satisfaction that adhesions are much less common since I have been routinely doing the low cervical operation.

In the cases which we reviewed there were three ruptured uteri. All were recognized and operated upon before rupture was complete and all babies were saved. One patient had had a previous classical section, one a low cervical, and the other apparently a hybrid of the two. This is not statistically conclusive. We all recognize, however, that meticulous technique and avoidance and control of infection lessen the danger of subsequent rupture.

The literature has repeatedly shown a greater incidence of ruptured uterus following the classical section. What is more important is that many of the ruptures occur before labor when the patient is not under hospital supervision. The same discrepancy in favor of the low cervical section is noted in mortality statistics.

This is the report of a master obstetrician in whose hands there is little difference in the results of the two operations. Much of the statistical disparity found in the literature is due to the fact that the casual and untrained operator follows the technique which is easier for him. More and more these operations are being done by the trained obstetrician and the disparity in results will be reduced as it has been in Dr. Falls' series. He has done an excellent and courageous job of pointing out to us that there is little excuse for an appreciable difference in the results of the two methods and his conclusions will hearten us when we feel that circumstances call for the classical operation.

But since the only objection raised to the low cervical section is that it is more difficult and since the tone of recent literature as well as our own experience tends to show that in the matter of adhesions and subsequent uterine rupture the low cervical operation has the advantage, most of us will continue to follow the Krönig technique.

DR. MILTON POTTER, Buffalo, N. Y.—No procedures could be compared in a more unbiased scientific method. Dr. Falls' final report, however, is no surprise to me. His paper should end the prolonged futile bickering which has been carried on for years and

which has thoroughly confused the medical profession. Let us now admit that both procedures are equally good in competent hands and let it go at that.

His paper gives me the opportunity to question the efficacy of the two layer continuous chromic catgut closure in the low cervical section and the three layer closure of continuous chromic catgut in the high classical section. I am aware that these terraced types of closures are usually used at the present time and I am also aware of their limitations.

Perhaps this is a good time for us to recall again and to heed the teachings of Drs. W. Wayne Babcock and J. W. Kennedy of this Association on the relation of wound reaction and lag of healing to chromic catgut suture material. We should also be reminded again that only harmful reactions can result from buried sutures which are ligatures and which crush the tissue in addition to being foreign bodies in a dead undrained space.

After an experience with 3,500 uterine closures as described by Dr. Falls, my father and I were far from satisfied with the over-all results. Since then, we have given much time and thought to a more effectual plan of uterine closure which could be applicable to both the high and low operation. This study resulted, 11 years ago, in a preliminary report, before this Association, of a technical method of closing the uterus which after 114 trials we felt constituted an improvement over the closures described here today.

Briefly, the technique consisted of using a single layer of interrupted silk sutures placed not too tightly in the outer third of the uterine wall after beveling the endometrial edges. To date we have experimented with this method in approximately 1,500 high classical sections with no maternal mortality, no uterine ruptures, and with only two cases which resulted in sinus tract formation.

I would like to suggest that some of the larger clinics give this closure technique a trial and report their observations at the next annual meeting. I hope at that time to present convincing evidence of my preliminary claims of 11 years ago.

DR. SAMUEL COSGROVE, Jersey City, N. J.—I agree with Greenhill's opinion as quoted by Dr. Falls, with the single exception that I do not recognize any significantly increased operative difficulty in doing the lower segment type of operation. Dr. Falls' maternal mortality can be dismissed, inasmuch as all of the deaths were due to causes quite independent of technical differences in operation. I would like to submit, however, the thought that Dr. Falls' two series represent only variations in the same operation; they do not represent corporal operations on the one hand, and cervical or lower segment operations on the other. He has stated that in patients not in labor the so-called lower segment operation as practiced by him sometimes involves the corporal segment. I would emphasize this point by stating that, except in cases very long in labor, such an incision *always* involves the upper or corporal segment. He is therefore talking only about two variants of the corporal operation, in one of which he reflects the bladder flap and places his uterine incision flaps a little lower. It seems to me that had he used the transverse incision of the lower uterine segment which is entirely within the lower uterine segment and does not involve the corporal segment, except in occasional cases usually before the completion of the pregnancy and in which there has been no labor, the results might have been a little more significant. I do not think that his paper gives a complete answer as to the possible superiority of the *true* lower segment operation as opposed to the corporal segment operation.

DR. K. S. RICHARDSON, Sydney, Australia.—I thought it might be interesting for you to know what we think of cesarean section in Sydney. Sydney is the capital of New South Wales, which has a population of two and a half million, of which one and a half million are concentrated in Sydney on the seaboard. We have one university in Sydney and attached to it are three obstetric teaching hospitals, King George V, the Women's, and The Royal Hospital for Women, I being on the Honorary Staff of the latter. Each hospital is handling approximately 5,000 confinements per year. The Professor of Obstetrics, Professor Bruce Mayes, is a very keen and ardent supporter of the lower segment operation, and this can be said of practically all the obstetric surgeons in Sydney.

First, let me say that I agree with Dr. Cosgrove. I prefer to call, or think of the procedure as a complete reperitonizing operation because the true lower segment is not present until labor is definitely established. I consider the lower segment operation to be, in most cases, the one of choice. First, because we are able completely to reperitonize the operation site and therefore make the consequent dangers of adhesions minimal. We find, also, that postoperative distention is less frequent than after classical section. I do not think it is a more difficult operation, although extraction of the child is slightly more involved. I consider the most difficult part of classical section, which was also mentioned by Dr. Henderson, is the neat repair of the upper uterine segment with accurate approximation of the serous surface, leaving a smooth edge so that omentum, bowel, and abdominal wall adhesions will be minimal. Because the lower segment operation aims at peritoneal covering I do not think that one has to go very low with the uterine incision. I make the peritoneal incision ½ to ¾ of an inch below where the peritoneum leaves its adherence to the uterus and a corresponding uterine incision. Consequently, there is no great need to traumatize the junction of bladder and uterine base. Pack it gently back and there is plenty of exposure. I maintain that a much easier delivery of the child is achieved by a transverse incision made slightly elliptical.

We endeavor to teach our students that cesarean section is not a "smash and grab" operation. Some surgeons in delivering a child remind me of the thief who throws a brick through a jeweler's window, puts his hand in, takes his loot, and runs. I consider that the baby can be softly and gently, and, I emphasize, slowly, extracted through an adequate transverse elliptical incision, sometimes with one blade of the forceps as the under lever to extract the head. Very occasionally it may be necessary with a head deeply engaged in the pelvis to make a further incision, vertical in type, forming an inverted T. I favor the lower segment operation in placenta previa. By incising the uterus down to the placenta and then gently finding the placental edge, the membranes can be ruptured.

We in Sydney agree that there is still a place for classical cesarean section where conditions in the lower segment, such as fibroids, or dense adhesions, might make opening of the bladder a possibility. Here discretion may be the better part of valor.

I make it a rule never to remove the appendix during cesarean section, as one of these surgical fields is potentially infective.

I have been very interested to hear Dr. Falls' paper and appreciate very much the long years of labor that he has spent in producing these figures; however, I must nail my colors to the mast as a firm believer in lower segment cesarean section.

DR. FALLS (Closing).—As regards Dr. Henderson's question of adhesions following the classical operation, I would say that adhesions result from peritonitis and according to our experience there was neither more postoperative pain nor postoperative ileus in the classical cesarean group.

We believe that there is no difference in the technical difficulty of the two operations since the average operating time in both series was identical. The reason we made the longitudinal incision and did not use the transverse incision as brought out by Dr. Cosgrove was that from the time the series was started 26 years ago there has been no deviation from the technique as shown here today. It is true that in a few cases some of my residents have used some of the antibiotics but this has not been significant, as they have been used in one group as much as in the other. No deviation was made in placenta previa cases in favor of the classical operation even when we knew it was necessary to incise through the placental site.

Statistics on rupture of the uterus seem to show, it is true, more ruptures after the classical operation. It is also true that the results following any operation depend largely on who did the operation. The only way to prove absolutely which operation is the best is to repeat this work. We believe, however, that if there were a difference in the results of the operation it would have shown up in this experiment.

ACUTE ADRENAL CORTICAL FAILURE AS A CAUSE OF SHOCK AND DEATH*

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WE ARE reporting our experience with acute adrenal cortical failure as it has appeared under a variety of circumstances in gynecology and obstetrics. The information gained from this study has convinced us that adrenal cortical failure may be a cause of shock and death, even though the patient may have been in apparently normal health before an episode of trauma. The six cases reviewed have presented essentially the same clinical syndrome. There were three fatalities, and necropsy data have established death as attributable to failure of adrenal cortical function. The three remaining patients presented a similar syndrome, but recovered after treatment with cortical substances. These cases are being reported with the hope that emphasis on the syndrome of acute adrenal cortical failure as a complication of surgery and other forms of stress will lead to its earlier recognition and treatment.

There is still no unanimity of opinion as to the role of the adrenal cortex in shock. Selye's[1, 2] theory of adaptation with its alarm reaction is gaining in popularity. It has been observed that shock is frequently a prelude to death in individuals with meningococcic meningitis; at autopsy the adrenal glands often show internal hemorrhage.[3] It is also known that the patient who has an adrenal tumor surgically removed may die in postoperative shock that is unrelated to blood loss. In this case, the opposite adrenal gland is frequently atrophic. It has been postulated that many persons have adequate adrenal function to carry on normal activities, but when the adrenals are confronted with the added stress of trauma, surgery, or infection, they are incapable of secreting sufficient hormones to maintain the organism throughout the crisis.

Postoperative deaths accompanied by shock and hyperpyrexia unassociated with blood loss have often been called "liver deaths" or deaths caused by the "hepatorenal syndrome." During World War II, one of the authors (E. S. T.), while a surgeon in an evacuation hospital, noted a number of postoperative deaths which occurred 24 to 72 hours after trauma and surgery. Viewed in retrospect, these deaths were frequently preceded by the same syndrome which is being discussed today. Massive blood transfusions and other supportive measures for the treatment of this type of shock were of no avail. The end result was death in each instance. Autopsy findings were of no aid except for the finding of cloudy swelling of the liver and destruction of tubular epithelium of the kidney.

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Theory and Physiology

There have been approximately 26 steroids isolated from the adrenal gland.[4] The adrenal cortex has many functions (Fig. 1). It regulates the distribution and excretion of electrolytes, particularly sodium, potassium, and chloride, and is therefore an essential organ in water balance. The adrenal cortex also plays an important role in the anabolism and catabolism of fats, carbohydrates, and protein. An important function which has been applied as a test of adrenal adequacy is its effect on the circulating eosinophils, lymphoid, and thymus tissues.

Adrenal cortical insufficiency may be of two types, primary or secondary. The primary type is caused by disease or disturbed physiology of the adrenal gland itself; the secondary type by inadequate secretion of adrenocorticotropic hormone (hereafter called ACTH) from the anterior pituitary gland, either as a result of disease of the anterior lobe of the pituitary gland or of the hypothalmus.

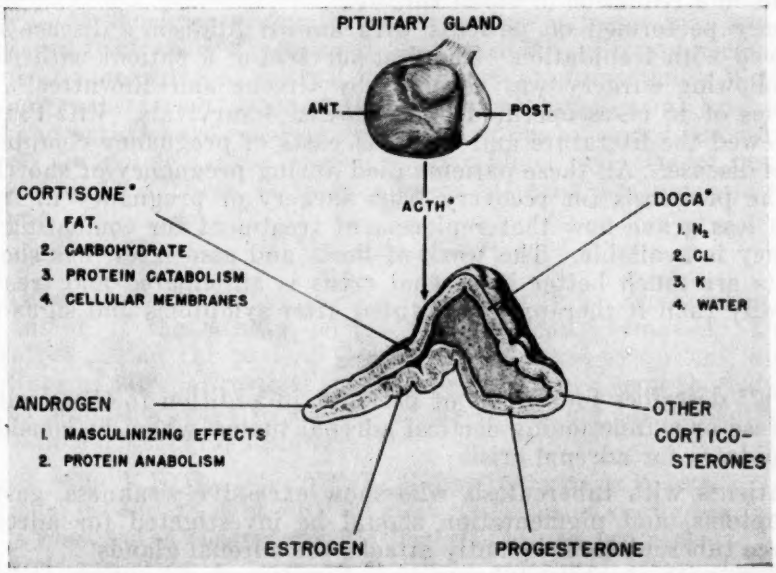

Fig. 1.—Physiological relationships of the anterior pituitary gland and the adrenal cortex, and functions of the adrenal cortex.

Selye's[1, 2] theory of the general adaptation syndrome seems best to explain adrenal cortical physiology under stress. He divides the syndrome into three phases. The first is the alarm reaction in which, following some type of stimulus or stress, the adrenal gland responds to combat the effects of the stimulus. The second stage is that of resistance in which adaptation to the stress is thought to be sufficient. The third and final stage is the stage of exhaustion in which the acquired adaptation is lost, and it is in this stage that postoperative adrenal cortical failure may occur, as illustrated by our Cases 2 and 5.

Venning, Hoffman, and Browne[5] found that individuals exposed to the stress of surgical procedures excreted from 3 to 30 times the normal amount of cortical substances in the urine. Crile[6] stated that, in patients who die in shock, microscopic evidence of disintegration of nuclei with granulosis within

*Adrenocorticotropic hormone (ACTH); desoxycorticosterone acetate (DCA); corticosterone (cortisone).

the cell membranes in the adrenal cortex is evident. Coppinger and Goldner[7] have demonstrated that the number of circulating eosinophils is directly related to the length and severity of surgical operative trauma.

The effect of administering adrenal cortical extract and desoxycorticosterone acetate (DCA) both before and after trauma in lowering the mortality rate in experimental shock after intestinal manipulation in normal rabbits has been demonstrated by Weil, Rose and Browne.[8] Perla, Freiman, Sandberg, and Greenberg[9] demonstrated the efficacy of saline and cortical hormone in the prevention and treatment of histamine shock in rats and mice. Weil and Browne[10] showed that the excretion of cortin in the urine increases to a maximum between the third and fifth day following surgery. They believe that this is a manifestation of response to a stimulus by an increased secretory activity of the adrenal cortex. Swingle[11] states that absence of adrenal cortical hormones causes general capillary atony, dilatation, and stasis in animals, which secondarily results in greater capillary permeability. Shock following adrenalectomy is initiated by loss of plasma through capillaries and this results in a reduction of blood volume.

Surgery performed on patients with known Addison's disease has long been viewed with trepidation. The first survival of a patient with Addison's disease following surgery was reported by Greene and Rowntree[12] in 1933. Their series of 15 cases operated upon showed 4 survivals. Fitz-Patrick[13] in 1922 reviewed the literature and found 11 cases of pregnancy complicated by Addison's disease. All these patients died during pregnancy or shortly thereafter. The prognosis for recovery from surgery or pregnancy in Addison's disease is less grave now that replacement treatment for combating adrenal insufficiency is available. The work of Perla and associates[9] has shown that the results are much better if adrenal crisis is anticipated and treated prophylactically than if therapy is instituted after symptoms and signs develop.

Diagnosis

Thorn[14] describes four types of patients, in addition to those with Addison's disease or a functioning cortical adrenal tumor, whom he considers possible candidates for adrenal crisis:

1. Patients with tuberculosis who show excessive weakness, gastrointestinal symptoms, and pigmentation should be investigated for adrenal adequacy since tuberculosis frequently attacks the adrenal glands.
2. Those with chronic nephritis who show low serum sodium and improve dramatically on high-salt diets.
3. Any patient of a dark-skinned race whose normal pigmentation may mask the pigmentation seen in adrenal insufficiency.
4. Those patients in prolonged shocklike states following surgery, trauma, or illness without other explanations for their shock.

The main purpose of this paper is to call attention to the syndrome of acute adrenal cortical failure. Our experience has impressed us with the importance of the following diagnostic signs, symptoms, and laboratory findings:

1. Delayed shock unrelated to depleted blood volume and unresponsive to blood replacement.
2. Marked hypotension.
3. Rapid pulse.
4. Cyanosis of fingers, toes, neck, and face.
5. Profuse diaphoresis.
6. Pain and tenderness over kidneys.
7. Extreme thirst.
8. Hyperpyrexia.

9. Mental confusion followed by disorientation and coma.
10. Oliguria or anuria.
11. Cold and clammy skin.
12. Elevated level of nonprotein nitrogen in the blood.
13. Increased serum potassium.
14. Decreased serum sodium and chlorides.
15. Albuminuria.

These 15 factors may not all be present in each patient; however, most of the signs, symptoms, and laboratory data here listed appear as part of the clinical syndrome if the crisis runs its course to death. The delayed shock, accompanied by cyanosis of the hands and feet, and the profuse diaphoresis have been particularly characteristic of the syndrome.

Acute adrenal cortical insufficiency should not be used as a general diagnostic file for deaths due to unknown causes. Pulmonary embolus, atelectasis, cerebral vascular accidents, blood loss, and many other insults to the physiology and anatomy of the individual can produce shock. We believe that this is one type of shock occurring in postoperative patients that has not been differentiated from other causes of shock and death. Prompt recognition and treatment of acute adrenal cortical insufficiency are important. We have used cortical adrenal extract successfully to combat hypotension and borderline states of shock that have resulted from some of our extended radical operative procedures for pelvic cancer when adequate blood replacement has failed to control the shock. These patients' clinical histories are not being reported at this time.

Case Reports

The first case of adrenal cortical insufficiency occurred when a masculinizing tumor of the adrenal cortex was surgically removed. During the postoperative period the patient developed the signs, symptoms, and laboratory findings of adrenal cortical insufficiency, and died soon thereafter. Postmortem examination revealed atrophy of the remaining cortical adrenal tissue. A brief résumé of this case follows:

CASE 1.—(St. J. H. No. 165055) E. S., a 37-year-old gravida ii, para ii, was admitted to the hospital on Aug. 18, 1950, with the chief complaints of amenorrhea for five years, a change in voice, and an acquired male distribution of hair for two years.

Physical examination on admission revealed a generalized hypertrichosis with male distribution and a blood pressure of 210/110. On Aug. 19, 1950, an adrenal tumor measuring 9 cm. by 12 cm. was removed. This proved to be a carcinoma of the adrenal cortex. The patient received 1,000 c.c. of whole blood the day of surgery. On the day of operation her blood pressure ranged from 100/70 to 125/90 and her pulse from 110 to 120 per minute. In spite of 4,000 c.c. of parenteral fluid, the urinary output was but 450 c.c. Twenty hours after surgery the blood pressure was 100/60 and the pulse was 120. Adrenal cortical insufficiency was suspected and she was given DOCA on the second and third postoperative days. Diaphoresis was marked but the patient felt warm and was alert. Until the fifth postoperative day she seemed to be doing fairly well and her blood pressure varied around 120/80. Her only complaint was thirst. It was then noted that the patient appeared tense and restless. She was noted to be having visual and auditory hallucinations. Following this she became markedly dyspneic and her blood pressure was unobtainable. The pulse was weak and thready at 140 per minute, she was completely disoriented, and the skin was warm. The urinary output was diminished. She was again given adrenal cortical substance and intravenous saline solution and seemed to improve. The following day her blood pressure was again unobtainable and the pulse was 140. Her skin was cold and clammy and her temperature rose to 104° F. The blood pressure was unobtainable for 20 hours and the pulse was rapid and feeble during that time. Massive doses of adrenal

cortical extract brought about some improvement for 36 hours and then again the blood pressure dropped, the pulse became weak, respirations were labored, cyanosis was evident, diaphoresis reappeared, and she died on the eighth postoperative day.

Postmortem examination revealed atrophy of the right suprarenal gland; surgically removed left adrenal gland; hyperplasia of the anterior lobe of the pituitary gland and of the pineal gland; congestion of the liver; and congestion and edema of the kidneys with cloudy swelling and degenerative changes of the tubular epithelium. Comparison of the high-power microscopic views of the cells of the adrenal cortex of this patient (Fig. 2) with cells of the adrenal cortex of a normal gland (Fig. 3) is quite striking. The normal cell has plentiful lipid material in its cytoplasm whereas the diseased gland exhibits cytoplasmic degeneration and nuclear pyknosis.

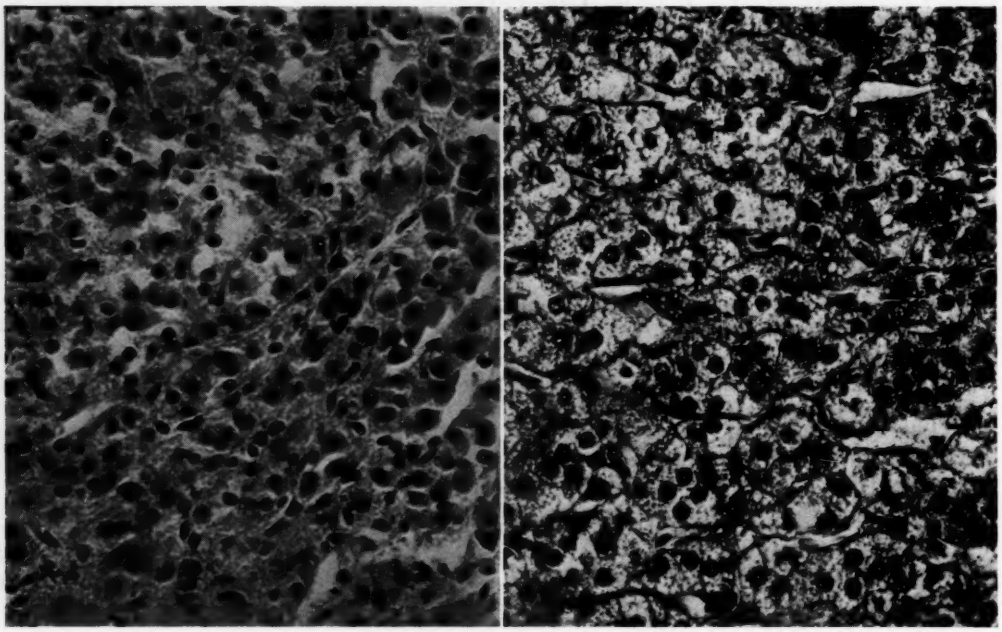

Fig. 2. Fig. 3.

Fig. 2.—Microscopic view of adrenal cortex, Case 1. Nuclear pyknosis, cytoplasmic degeneration, and lipid depletion are evident. The total cortex was atrophic. (×450).)

Fig. 3.—Microscopic view of normal adrenal cortex. The cell columns are distinctly arranged. The nuclei are large and granular. The cytoplasm is well supplied with lipoid material. (×450.)

Our second case occurred in a young woman who was apparently in good general health prior to a hysterectomy. Her postoperative course was strikingly similar to that of the previous patient. This death was ascribed to the "hepatorenal syndrome" after the autopsy data were completed. Further experience and study have led us to the conclusion that this patient died of adrenal cortical insufficiency.

CASE 2.—(C. G. H. No. 27376) L. J. R., a 26-year-old woman, gravida i, para i, was admitted to the hospital on Oct. 2, 1950, with a chief complaint of intermittent left lower quadrant abdominal pain of two years' duration. Since the birth of her only child, five years before, she had been having irregular menses with episodes of prolonged bleeding.

The physical examination was essentially negative except for the pelvic findings. The cervix was long and firm; the fundus was indistinguishable from an irregular mass which occupied the pelvis and left adnexal region. A dilatation and curettage were followed by a laparotomy under general anesthesia, at which time a large endometrial cyst

was found that filled the cul-de-sac of Douglas. Both tubes and the left ovary were involved. A total hysterectomy and left salpingo-oophorectomy and right salpingectomy were performed. On the day of surgery she received 500 c.c. of whole blood and 2,000 c.c. of 5 per cent glucose in water. On the first postoperative day she received 3,000 c.c. of 5 per cent glucose in water. Throughout this day and evening, the patient was in excellent condition. Shortly after midnight, and approximately 36 hours following surgery, the nurse found the patient to be cold, clammy, and cyanotic. The pulse and blood pressure were unobtainable. In spite of this, the patient said she felt perfectly well except for thirst and back pain and she was well oriented. The lungs were clear and the abdomen was soft. There was minimal abdominal distention and no evidence of bleeding.

The patient was placed in Trendelenburg position and in an oxygen tent. A venous cut-down was performed and 1,000 c.c. of 5 per cent glucose in water was started. Fifty mg. of ephedrine brought the systolic pressure to 90 mm. of mercury and the pulse was 100 for a short time. A blood count at this time revealed 13.5 Gm. of hemoglobin and 5.8 million red blood cells.

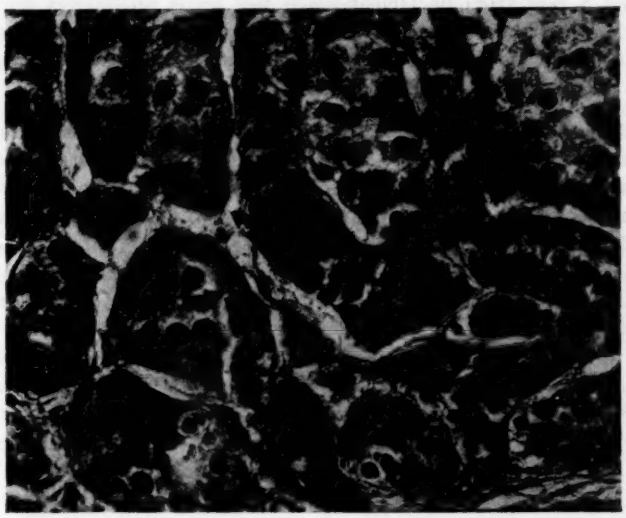

Fig. 4.—Microscopic view of adrenal cortex, Case 2. A decrease in lipids and disintegration of cytoplasm are seen. Gross examination revealed thinning of both adrenal cortices. (×450.)

Six hours following the initial episode of shock the pulse and blood pressure were again unobtainable, the patient was mentally confused, and the rectal temperature was 106° F. She faded into coma and became more cyanotic. The respirations became increasingly labored, the diaphoresis was more marked, and she died 46 hours postoperatively.

The significant autopsy findings were as follows: The adrenal cortices were thinned. The fascicular zone showed a decrease in lipids, and disintegration of cytoplasm (Fig. 4). The liver sections revealed severe fatty metamorphosis. The kidneys appeared normal and the lungs showed some hyperemia and edema.

The next two case reports are those demonstrating adrenal cortical failure associated with septicemia. A diagnosis of a Waterhouse-Friderichsen syndrome[3] (adrenal cortical failure due to sepsis) was made in each of these patients and specific therapy was instituted. Both patients recovered, and an eosinophil response to ACTH confirmed the diagnosis in one. The diagnostic test was not performed in the other, but the eosinophil count was suggestive of latent adrenal insufficiency.

CASE 3.—(D. G. H. No. 273190) M. C., a 24-year-old Spanish-American woman, gravida iv, para ii, whose last menstrual period was in November, 1950, was admitted to the hospital on Feb. 10, 1951, with chief complaints of vaginal bleeding for three days, chills, fever, and abdominal cramps. She passed a fetus in the emergency room soon after admission to the hospital. The admitting diagnosis was septic abortion.

Physical examination on admission revealed an acutely ill woman whose temperature was 105° F., pulse 116, respirations 28 per minute, and blood pressure 84/56. She was given penicillin, streptomycin, and intravenous fluids. Several hours after admission the blood pressure dropped to 60/40. Blood loss was not marked. The patient's skin became cold and clammy with marked diaphoresis and she complained of thirst and backache. She was mentally clear. Blood, intravenous fluids, including saline and adrenal cortical extract, were given. There was no urinary output during the first 24 hours in the hospital. The nonprotein nitrogen was 63 mg. per cent and the serum sodium 15.7 mg. per cent. Her condition remained critical for 48 hours and then she began to improve. The adrenal cortical extract was gradually decreased as her condition became stabilized and was discontinued on Feb. 22, 1951. A Thorn test, after the patient's recovery, was positive in that ACTH stimulation caused a rise from 95.2 eosinophils per cubic millimeter of blood to 143 per cubic millimeter in four hours, indicating functional impairment of the adrenal cortex. On March 2, 1951, a uterine curettement was performed and her postoperative course was uneventful. She was discharged on March 6, 1951, in good condition.

CASE 4.—(D. G. H. No. 278458) L. W., a 33-year-old gravida vi, para v, white woman, whose last menstrual period was July 19, 1951, was admitted to the hospital on Sept. 9, 1951, with the chief complaints of malaise, chills, and fever. On admission to the hospital the physical examination revealed a temperature of 105.4° F., blood pressure 104/60, and a pulse rate of 132 per minute. The uterus was three times normal size and the cervix was soft. The remainder of the physical examination was essentially negative. She was started on penicillin and streptomycin and later given aureomycin and Gantrisin. Shortly after admission, there was a precipitous drop in blood pressure to 40/0 for no known reason and the pulse rate remained at 132 per minute. There was no vaginal bleeding present. She complained of nausea and backache and appeared lethargic and cyanotic. Laboratory studies revealed: hemoglobin 10.5 Gm., hematocrit 37, total eosinophils 106.4 per cubic millimeter, blood chlorides 590 mg. per cent, and a positive blood culture for *E. coli* was obtained. Her urinary output for the first eight hours was 475 c.c. after she had received 2,000 c.c. of intravenous fluids. She was given adrenal cortical extract which was continued for four days. She continued to improve and was discharged as recovered on Sept. 17, 1951. The discharge diagnosis was septic abortion complicated by adrenal cortical insufficiency.

The next patient developed a shock state 57 hours after hysterectomy. The signs and symptoms exhibited led to a diagnosis of acute adrenal cortical insufficiency. Prompt treatment with adrenal cortical extract, cortisone, and DCA produced dramatic recovery. A Thorn test, done postoperatively, for adrenal cortical insufficiency, showed that this patient had impaired adrenal cortical function that was not suspected before surgery.

CASE 5.—(C. G. H. No. 45505) E. T., a 35-year-old nulliparous, mentally defective white woman, was admitted to the hospital on June 25, 1952, because of the presence of a large abdominal tumor mass.

The pertinent physical findings on admission were as follows: blood pressure 130/90, pulse 70, respirations 32, and temperature 100.2° F. There was an increased amount of hair on the chin and upper lip. Abdominal examination revealed a large, irregular, movable mass arising from the pelvis.

On June 27, 1952, the patient was taken to surgery; a large pedunculated leiomyoma was found, and a total hysterectomy was done under general anesthesia. Following surgery the patient received 3,000 c.c. of subcutaneous 5 per cent glucose in distilled water and seemed to do well. She complained of severe thirst and demonstrated moderate diaphoresis. Her blood pressure was 110/70.

At 7 P.M. on June 29, 1952, approximately 57 hours after surgery, she was noted to be in a state of shock. The skin was cold and clammy, the nailbeds of the fingers and toes were cyanotic, the lips and face were dusky, radial pulse and blood pressure were unobtainable, and the temperature was 103.2° F. There was no urinary output during the previous 15 hours. Blood chemistry studies revealed a serum sodium of 125 meq. per liter, potassium 4.6, and chloride 86.8 meq. per liter. The carbon dioxide combining power was 53 volumes per cent. She was given aqueous adrenal extract, desoxycorticosterone acetate, cortisone, whole blood, and saline. The blood pressure increased to 110/80 and the urinary output increased considerably. The cortical substances were continued with gradually decreasing doses and were discontinued completely on July 5, 1952. She continued to do well and was discharged on July 14, 1952. A Thorn test done before she was discharged from the hospital revealed an initial eosinophil count of 198 per cubic millimeter of blood and 220 eosinophils per cubic millimeter four hours after ACTH.

The last case report is that of a patient who developed anterior pituitary cachexia, secondary to abruptio placentae and fibrinolysis. Adrenal cortical atrophy was demonstrated at autopsy. Review of this patient's course reveals that her episode of shock was caused by adrenal cortical failure which was secondary to a lack of essential ACTH stimulation to the adrenal cortex from the anterior pituitary gland. Her clinical course was typical of adrenal cortical failure. The syndrome was recognized initially but disagreement among the consultants led to a change in the diagnosis and a discontinuation of specific therapy. This patient should have been treated with ACTH and adrenal cortical substances.

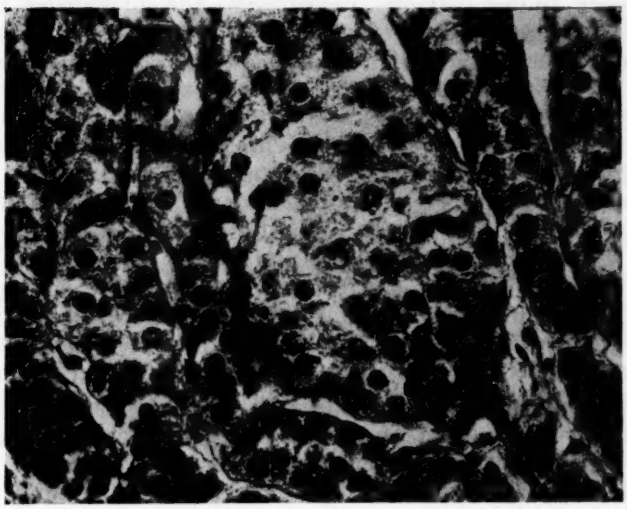

Fig. 5.—Microscopic view of adrenal cortex, Case 6. There are partial obliteration of the columns, nuclear pyknosis, and cytoplasmic disintegration. The cell content of lipids is markedly reduced. (×450.)

Gross examination of the adrenal cortices showed bilateral atrophy.

CASE 6.—(C. G. H. No. 43845) J. B., a 35-year-old gravida iv, para iii, white woman, was first seen in the emergency room on March 23, 1952, approximately 38 weeks pregnant and having had no prenatal care. Her complaint on admission was abdominal pain. After examination the diagnosis of pre-eclampsia and abruptio placentae with associated fibrinopenia was made. The plasma fibrinogen level was 0.08 Gm. per cent. She was given 4 Gm. of fibrinogen and 2,000 c.c. of whole blood. After the shock secondary to blood loss was corrected the placental membranes were ruptured and intravenous Pitocin was given to induce labor and delivery. On March 24, 1952, she was delivered of a 2,375 gram stillborn male infant. On the day following delivery the blood nonprotein nitrogen was 45 mg. per cent, and the serum chloride was 87.6 meq. per liter. During the postpartum period

the patient had marked diuresis to 5,000 c.c. daily, and the nonprotein nitrogen level rose to 120 mg. per cent on the ninth postpartum day. Serum sodium, potassium, and blood chlorides were normal. During this time she showed gradual improvement except for daily fever of 102 to 103° F. On the ninth postpartum day she suddenly became unresponsive, the pulse was weak and thready at 130 per minute and the blood pressure was unobtainable. Marked diaphoresis was present, the skin was cold and clammy, but showed no cyanosis of the extremities. She was started on aqueous adrenal extract and Lipo-Adrenal and the following day showed signs of improvement. She became alert and warm, and the blood pressure was 130/84. The adrenal cortical extracts were continued for nine days. On the eleventh postpartum day the patient had a grand mal seizure involving the left side of the body. Spinal tap revealed bloody spinal fluid. Following this she seemed to improve gradually although she still showed marked diuresis. On May 1, 1952, she began to have hallucinations and paranoid thoughts. On June 3, 1952, she had another convulsion with resultant left hemiparesis for 12 hours. On June 11 she suddenly went into shock but did not respond to blood transfusions and Adrenalin. At this time the blood chlorides were 135 meq. and the blood sugar 74 mg. per cent. She remained semistuporous, breathing rapidly, with pulse 160 per minute and blood pressure 102/80. She died on June 12, 1952.

At autopsy the pituitary gland, adrenal cortices, thyroid gland, pancreas, and ovaries were found to be atrophic. The endometrium and vaginal epithelium also showed atrophic changes. Adrenal cortical cells revealed decreased lipids and degeneration of nuclei and cytoplasm (Fig. 5).

Treatment

Although the methods of treatment and the dosages used may vary for different patients under various conditions, the principles of therapy are similar. The problem is either to substitute for or to stimulate the secretion of adrenal cortical substance. There are several cortical preparations which may be used but the pharmacologic properties of each are different. The whole aqueous cortical extract has a low potency and short duration of action so that it should be given in repeated divided doses. Very large doses of this preparation can be given without the danger of overdosage. Lipo-Adrenal Cortex is prepared partly from hog adrenals and partly by synthesis. Its main constituents are the 11 oxysteroids and, therefore, it has a great influence on carbohydrate regulation but less on sodium- and chloride-retaining capacity. On the other hand, DCA has a great influence on the sodium and chloride retention and potassium excretion but little carbohydrate regulatory activity. Cortisone has little salt-retaining ability but increases the metabolism of fat, thereby causing the body to utilize less carbohydrate. ACTH is of little value in the treatment of the primary type of cortical insufficiency.

The therapy recommended for acute adrenal cortical insufficiency in the postoperative patient or in the septic patient is the same as that advocated by Thorn.[14] The dosage may have to be increased according to the response. Patients in crisis with Addison's disease or patients with latent Addison's disease in acute adrenal insufficiency following surgery, trauma, or infection should be treated vigorously. The aims of therapy in patients with adrenal insufficiency are several. Adrenal cortical substance must be substituted for that which is absent or deficient. Blood volume must be increased by parenteral fluids, plasma, or blood. Vasopressor substances may be used for raising the blood pressure. The supply of glucose and electrolytes, particularly sodium chloride, should be increased. The plan of therapy in these cases is as follows[14]:

1. Desoxycorticosterone acetate (DCA) in oil, 10 mg. intramuscularly, should be given immediately. This may be repeated in 12 hours. The patient should receive 10 mg. of desoxycorticosterone acetate in oil daily until the crisis is passed. In our own experience this hormone may be withdrawn after four to five days of treatment.

2. Cortisone, 100 mg., intramuscularly, is given immediately, and 50 mg. is repeated each six hours until the crisis has passed. The dose then may be reduced to 25 mg. twice daily. From this point the dose is gradually decreased and discontinued when it is felt the patient is out of danger.

3. Aqueous adrenal cortical extract, 30 c.c. intravenously, is given immediately. During the first 12 hours, an additional 30 c.c. of aqueous adrenal cortical extract is given intravenously, in 1,000 c.c. of 10 per cent glucose in saline. Repeated doses of aqueous adrenal cortical extract are given as the patient's condition warrants it.

4. If dehydration is severe, adequate parenteral fluids should be given along with the electrolytes in order to try to keep proper fluid and electrolyte balance. When the patient is able, she should be allowed fluids by mouth.

In patients who are to undergo adrenal surgery, Thorn[14] advocates the following preoperative preparation: On the third day prior to surgery, the 48 hour ACTH test is begun and ACTH is continued up to the time of surgery. In this way the amount of adrenal cortical substance due to the ACTH stimulation is increased. Twelve hours before surgery 100 mg. of cortisone is given, and two to four hours preoperatively 50 mg. of cortisone is repeated. During surgery an intravenous drip of 5 per cent glucose in distilled water containing aqueous adrenal extract is given. On the evening following surgery 50 mg. of cortisone every eight hours is given. As the patient's condition warrants, the dose of cortisone is gradually decreased to 25 mg. twice daily by the sixth postoperative day. By the end of the second postoperative week the dose may be reduced by one-half. In patients in whom the cortical insufficiency is not so marked this dosage plan may be tapered off much more quickly. Adequate intake of sodium chloride is important particularly in the immediate postoperative period.

Summary

Six cases of acute adrenal cortical failure have been reported. Three patients died from the condition, and necropsy data proved adrenal cortical insufficiency as the cause of death. Three other patients presenting the same syndrome were treated for adrenal cortical insufficiency and survived.

The physiology of the adrenal cortex is reviewed as it relates to the surgical patient, and to the patient presenting signs of shock unrelated to blood loss.

The prevention, recognition, and treatment of cortical adrenal insufficiency are presented.

Conclusions

1. Unexplained shock states in the postoperative period or shock associated with sepsis may be due to acute adrenal cortical insufficiency.

2. Deaths from delayed postoperative shock hitherto ascribed to the "hepatorenal syndrome" or overwhelming sepsis may, in some instances, have been caused by unrecognized adrenal cortical insufficiency.

3. Shock caused by adrenal cortical insufficiency should not be confused with shock that results from hemorrhage, embolic disease, atelectasis, and other well-recognized causes of shock.

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Discussion

DR. THOMAS C. PEIGHTAL, New York, N. Y.—Dr. Taylor and Dr. Essig have reported six well-authenticated cases of adrenal cortical insufficiency from their practice in the past two years which point up its incidence. This proves the importance of possessing a sound knowledge of this complication and of the physiology of adrenal function and dysfunction as well as of acquiring a familiarity with the various preparations now available for therapy.

Experimentally much research has been done in this field over the past 25 years but the end result of it all—namely, the production of potent adrenal therapeutic agents in quantity—has come to the profession generally only in the past 5 years. Thus to many of us, like myself, this subject of acute adrenal cortical failure as a cause of shock and death is comparatively new in our specialty and certainly the management of this complication deserves the considered attention of each one of us.

The essayist's description of the physiology of the adrenal cortex and the possible mechanism by which its dysfunction may produce severe degrees of shock is most informative. That this gland has many functions such as the distribution and excretion of electrolytes, particularly sodium, potassium, and chlorides, and thereby affects water balance; that it influences the handling of fats, carbohydrates, and protein; that it affects the capillaries and their contents have been stressed to lay the background for the logical therapeutic attack on adrenal shock which has been so carefully detailed in this paper.

The six cases reported are particularly instructive since they illustrate the various types of "trauma," so-called, which had produced the adrenal deficiency. Two cases occurred in the presence of sepsis (the Waterhouse-Friderichsen syndrome); one developed latently after the immediate shock from hemorrhage of an abruptio placentae with fibrinolysis had been overcome and was thought to have been an example of secondary adrenal failure due to anterior pituitary cachexia; two were examples of potential adrenal insufficiency which went on to adrenal shock after the trauma of complete abdominal hysterectomy; and one patient, following the removal of an adrenal tumor, went into latent shock when the remaining adrenal gland proved inadequate from atrophy.

This paper teaches us much as to both substitution and stimulation therapy and particularly emphasizes the attention one should give to the all-important prophylactic therapy when indicated. Stating that the pharmacologic properties of each major type of cortical preparation are different in their constitutional effects, the authors describe these properties in detail. For this reason three preparations, desoxycorticosterone acetate, cortisone, and aqueous adrenal cortical extract are used together in most instances where acute adrenal cortical insufficiency occurs and the customary dosages of each are stated.

DR. E. C. HUGHES, Syracuse, N. Y.—Acute adrenal insufficiency is rare during pregnancy because the adrenal cortical function is increased as demonstrated by the fact that the corticosterone excretion is twice as much in the pregnant woman as in the nonpregnant one. However, if the patient possesses adrenal glands of low reserve, failure can occur during pregnancy. It can also happen in women with low reserve adrenals, after stress

of major or even minor pelvic surgery or intensive irradiation. The diagnosis is difficult to make in these individuals before failure but surely it should be completed soon after.

Although the diagnosis is made generally upon physical findings, as has been chiefly done by Dr. Taylor, it can be substantiated by certain laboratory tests. Because of the decrease in plasma volume, there are certain changes which take place in the blood which are significant. They are as follows:

1. There is a false elevation in the hematocrit, red cell count and hemoglobin estimation. This change was noted in Case 2 of Dr. Taylor's series.
2. Plasma sodium and chloride and carbon dioxide combining power are generally decreased in spite of the hemoconcentration.
3. Plasma potassium is generally elevated. This can be detected by noting a high pointed T wave and the low P wave in electrocardiographic tracing.
4. There is an increase in the blood urea and the nonprotein nitrogen levels which is due to the mild renal insufficiency caused by lower glomerular filtration.
5. The hypoglycemia can be detected by the blood sugar determinations.
6. The estimation of the total corticosteroid excretion during the failure period may give important information as to the degree of failure.

Adrenal crisis may also occur in women suffering from obscure chronic adrenal insufficiency. This group are often considered complainers, malingerers, and pass from one doctor to another. Certain laboratory tests are more specific in this group. Inasmuch as these patients do not handle water well, the Robinson, Power, Kepler water test is of value. The eosinophil response to epinephrine and ACTH is helpful. The estimation of the 17-ketosteroids is an excellent determination of adrenal cortical function in women particularly, because all of this hormone comes from this structure in the female.

In Case 1 of Dr. Taylor's series, 17-ketosteroid determinations would have been of definite value. This together with pyelography would have confirmed the diagnosis of adrenal tumor prior to operation.

After diagnosis, the treatment of acute adrenal insufficiency represents a serious medical emergency. Without vigorous therapy, these patients are not likely to survive. If one understands the physiology involved, the treatment is rather specific:

1. The correction of the hypoglycemia is carried out by the administration of glucose solution, usually in saline, intravenous cortical extract, cortisone and cortical extract, intramuscularly.
2. The hyponatremia, hypotension, shock, and vascular failure are controlled by the administration of intravenous salt solution to restore the blood volume and the administration of desoxycorticosterone to cause a retention of salt. The amount of sodium chloride administered should be at least 20 Gm. in physiological concentration. In some instances it may be necessary to give even more than this.

If there is any criticism to be made of Dr. Taylor's cases, it would be that not enough sodium chloride had been given. It was noted that most of the glucose had been given in distilled water. There is some question as to whether the adrenal failure had not been increased in several of the patients, because of too much water.

This brings up an interesting point in respect to the use of glucose-salt and water during and immediately after operation. Perhaps if we were to survey our patients more specifically before operation, we would choose the supportive materials which we would use more carefully. In some patients, glucose should be used in water, while in others sodium chloride should be added. It is well to remember that there is relatively little danger of overtreatment in patients who are in Addisonian crisis. These patients generally die from insufficient therapy. Once the patient is out of crisis, however, danger of overtreatment must be considered.

We have had five patients who have exhibited adrenal insufficiency—three following delivery, one during pregnancy, and the other following a simple gynecologic procedure. I would like to discuss briefly the latter case.

This patient was a 59-year-old woman, para ii, who stated she had never been ill until six months prior to admission to the hospital. During the past six months, however, she had been a patient in three other hospitals. She had had barium enemas, gastrointestinal series, complete studies of the kidneys, and other types of studies which showed nothing pathological. On Nov. 10, 1949, she was admitted to one of the hospitals for biopsy of the cervix. Except for a noted hypotension, the general physical condition of the patient was good. Under intravenous Pentothal, she was proctoscoped and a biopsy of the reddened area of the cervix was taken. Twelve hours later the patient became pulseless, the blood pressure dropped to zero, and there was a slight cyanosis, marked dyspnea, and profuse diuresis. The blood pressure improved to 78/65 during the next 24 hours. This shock picture remained for a period of about 2 weeks. She was then removed to the service of the Syracuse Memorial Hospital where she was studied more completely by Dr. Charles Lloyd. The blood count revealed 16 Gm. of hemoglobin, 4.8 million red blood cells, marked increase in the eosinophil count. The blood sugar was 100 mg. per 100 c.c. and nonprotein nitrogen was 97 mg. per 100 c.c., and carbon dioxide combining power was 32 volumes per cent. There was an abnormal T wave on electrocardiographic tracing. Total adrenal corticosteroids were below normal until one day prior to death when they increased to above the average. Three days after admission, although adequate hormone therapy had been instituted, the patient suddenly died.

Autopsy revealed a diffuse lymphatic hyperplasia throughout the body and a bilateral adrenal atrophy.

DR. ARTHUR B. HUNT, Rochester, Minn.—I should like to reiterate a warning that I am sure many of you have heard that patients on cortisone or ACTH for various medical conditions may occasionally have it withdrawn if they are transferred from a medical to a surgical service and are therefore in a state of hypoadrenalism when they go to surgery. The course of cortisone should be continued through the operative and postoperative period. Otherwise such patients undergo surgery in a state of hypoadrenal function and are liable to the type of severe postoperative collapse Dr. Taylor has so well described. After one or two near disasters our group learned the importance of this fact.

A second comment concerns an obstetric patient I delivered about six weeks ago who had had a bilateral adrenalectomy before her pregnancy because of a bilateral pheochromocytoma producing a severe hypertension. This woman was carried through pregnancy very nicely on the usual substitution care as has been outlined by Dr. Taylor and others of cortisone, DOCA, and salt with varying doses throughout her pregnancy, and did very well. We were prepared, of course, for such a collapse as Dr. Taylor mentioned and had noradrenalin, a powerful hypertensive drug, as well as intravenous cortisone available. When the patient went into labor she was given 100 mg. of cortisone in addition to what she had been taking and went through labor, delivery, and the postpartum period without any unusual event. The importance of such cases, I think, rests in the fact that now that proper supportive treatment by these agents mentioned is available, patients go through pregnancy and delivery with very gratifying safety factors that they did not possess before. Before this therapy was available around 75 per cent of pregnant patients with Addison's disease died within six months of the postpartum period.

DR. TAYLOR (Closing).—Dr. Hunt has given you valuable clinical information concerning the pregnant patient following bilateral adrenalectomy, and concerning the surgical risks surrounding the patient who has been on cortisone treatment. Drs. Peightal and Hughes have emphasized many things that I was not able to cover in my allotted time. I would like to reiterate what Dr. Hughes has already mentioned in the matter of intravenous saline. I find that as we leave our postoperative fluid management mostly to the junior house staff, somewhere along the line in their medical-school careers they have been told about the dangers of too much sodium chloride, so they do not administer any. Instead, they give only glucose and distilled water. I think that it is perfectly possible to send a patient into this type of collapse, if she has a latent adrenal cortical insufficiency, by withdrawing the saline completely. That is the manner of producing an Addisonian crisis.

THE EFFECT OF ESTROGENS AND OTHER STEROIDS ON THE PITUITARY GONADOTROPHINS IN WOMEN*

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THE effect of estrogens on the pituitary has been extensively studied. The great variety of experiments on laboratory animals and the many clinical studies have accumulated a tremendous fund of information. However, the interpretation of these observations and data has been difficult and often conflicting.

In general, two theories have been proposed, one that estrogens (and/or androgens) inhibit or suppress the gonadotrophic activity of the pituitary, while the other concept proposes that estrogens (and/or andogens) stimulate the production or release of the gonadotrophins.

Because of this confusion and incertainty regarding the role of estrogen in the pituitary physiology, it seemed desirable to embark upon an exploration of this problem by a complete reappraisal of the situation both in the experimental animal where direct information was available, and also in women by the indirect means at our disposal. Consequently, a series of experiments was devised which it was hoped would shed light on this problem. It is the purpose of this report to outline these experiments and to summarize those findings which have a bearing upon the problem of the relationship of sex steroids, particularly estrogen, to the physiology of the anterior pituitary.

Experimental animals are the only means by which direct information is available on the effect of estrogen on the pituitary itself. Consequently a series of rat experiments was designed by which the pituitary could be removed at autopsy and the content of gonadotrophin assayed directly. In women, indirect evidence was sought by studying changes in the ovarian cycle as reflected by weekly endometrial biopsies. In some of the experiments the excretion of pituitary gonadotrophic hormone in the urine as measured.

While estrogen is the most important steroid in the gynecologic endocrine physiology and pathology, similar studies were undertaken on testosterone and on androstenediol. Although studies on the latter group of substances were not as extensive as on estrogen, the observations are sufficiently complete to establish their probable relationship in women.

Procedure

The experiments on rats were as follows: 25- to 30-day-old female rats of the Sprague-Dawley strain were utilized for study. Estrogen in doses varying

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from 1.3 to 200 gammas was given as a single injection in 0.1 to 0.4 c.c. of sesame oil. The animals were autopsied from 48 to 120 hours following the injection of estrogen and the pituitary, ovaries, and uteri weighed. The pituitary glands were assayed on immature rats of the same strain, the dosage being administered over three days in such a fashion that a suspension of 1½ to 2 pituitary glands were injected into each test animal. The test rats were autopsied at 72 to 76 hours after the initial injection, and ovarian and uterine weights were determined; control rats were used with each experiment.

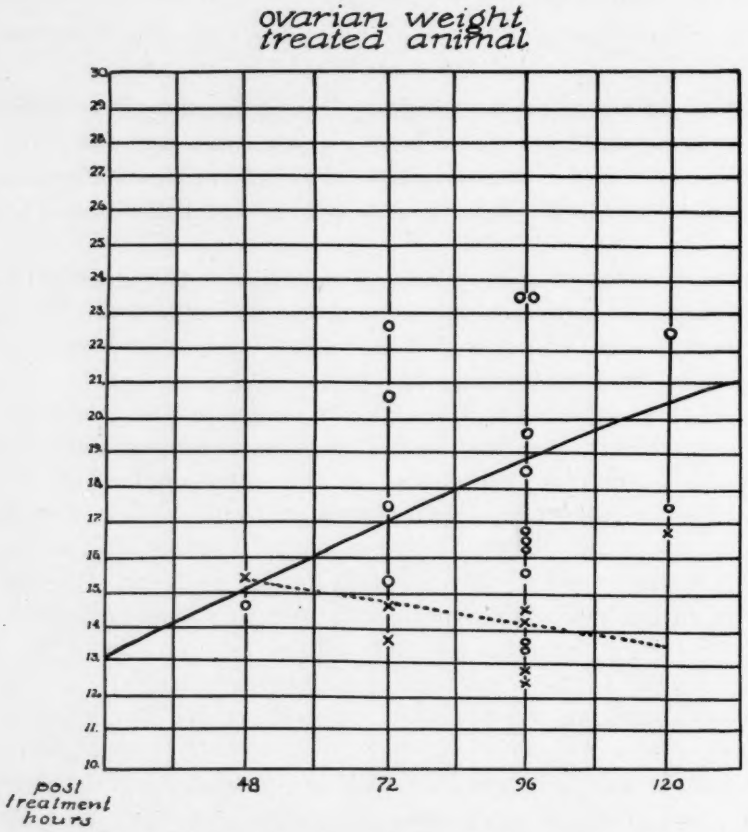

Fig. 1.—Symbols for Figs. 1-4. Estrogen was administered in varying doses and the animals autopsied at the intervals indicated. The *O* indicates weight of glands of treated animals and *X* indicates controls. The solid line represents the trend under treatment and the broken line, the control.

The ovarian weight of the treated animal rises following administration of estrogen, suggesting a release of gonadotrophin.

These data are presented in Table I and Figs. 1 to 4. When estradiol was given in doses of 2 to 20 gammas and the animal was autopsied 48 to 96 hours later, a progressive increase in the ovarian weight was apparent (Fig. 1) and seemed to be directly proportionate to the dose of estrogen and the posttreatment interval employed.

In the assay of pituitary potency (content), there seemed to be no significant change at 48 hours. However, at 72 hours, the concentration of gonadotrophin in the pituitary was considerably reduced as indicated by the decreased response of the ovary in the animals injected with a pituitary gland extract (Fig. 2). The weight of the pituitary gland, while varying considerably from

lot to lot of animals, showed a consistent increase throughout the 120 hours of the experiment (Fig. 3). (For details see Reference 1.)

These experiments indicate that there is an increase in the weight of the pituitary beginning approximately 72 hours after the injection of estrogen and continuing until about 96 hours. Second, between 48 and 96 hours after the injection of estrogen, there is a rise in the weight of the ovary of the treated animal, suggesting a release of the gonadotrophin from the pituitary. Third, the potency of the pituitary remained at parity through 72 hours, but thereafter the pituitary potency was reduced, suggesting that the gonadotrophin had been released. These experiments suggest that there may be an initial stimulation of the pituitary by estrogen which reaches a peak at approximately 96 hours and is followed by a release of gonadotrophin as manifested by an emptying of the gland and stimulation of the ovaries of the treated animals (Fig. 4 and Table I).

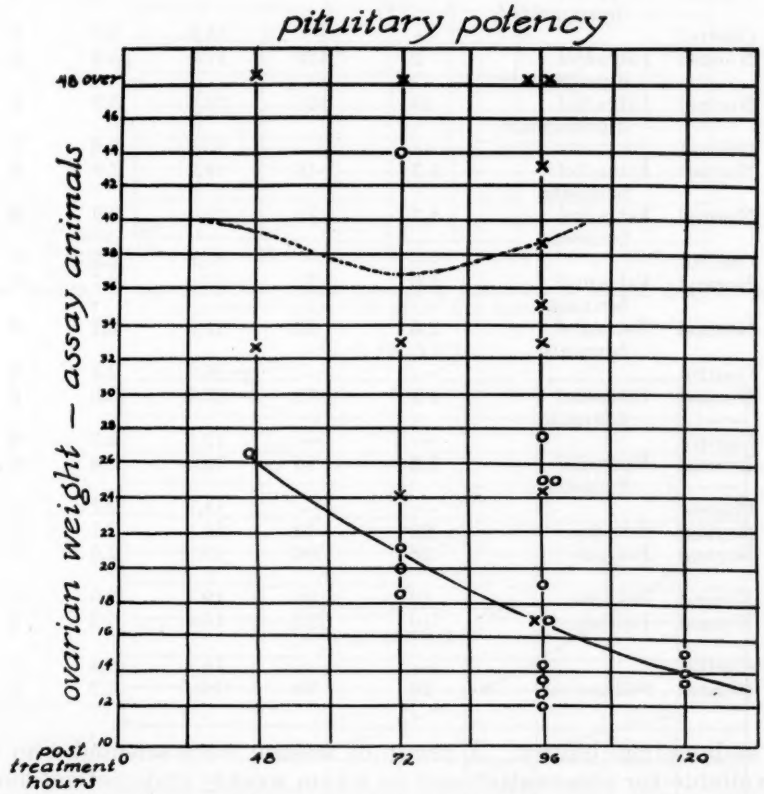

Fig. 2.—See legend, Fig. 1, for symbols. The pituitaries of the treated animals were removed at autopsy at intervals of 48 to 120 hours post treatment, and the gonadotrophin content assayed by injection into immature female rats. The weight of the assay animal ovaries decreased progressively following estrogen administration, indicating a depletion of the pituitary gonadotrophin content (potency). See text.

The experiments on women must of necessity be indirect. There is no satisfactory method of measuring the pituitary gonadotrophic content of the pituitary gland. One can measure the gonadotrophic hormone in the urine, but when studying urinary gonadotrophins it is necessary to take into account the normal variations in concentration throughout the ovarian cycle (Fig. 5). Perhaps more reliable and certainly more acceptable is the assay of the pituitary physiology by measuring the response of the human ovary as interpreted

TABLE I. OBSERVATIONS ON THE OVARIAN WEIGHT AND ON THE PITUITARY WEIGHT AND ITS GONADOTROPHIC HORMONE CONTENT IN NORMAL INFANTILE FEMALE RATS AFTER TREATENT WITH ESTROGENS IN VARIED DOSES FOR 48 TO 120 HOURS

EXPERIMENT NO.	NO. RATS	TREATEMNT			WEIGHT OF OVARIES (MG. AV.)	WEIGHT OF PITUITARY (MG. AV.)	ASSAY RATS	
		ESTROGEN	DOSE (GAMMAS)	TIME (HOURS)			NO. RATS	WEIGHT OF OVARIES (MG. AV.)
1	10 Control		—	—	12.9	2.1	5	32.9
	8 Normal	Estradiol dipropionate	2	96	13.5	2.8	5	12.0
	8 Normal	Estradiol dipropionate	20	96	16.7	3.0	5	18.9
2	8 Control		—	—	14.4	2.7	5	43.8
	8 Normal	Estradiol dipropionate	2	96	23.5	3.3	5	12.5
	8 Normal	Estradiol dipropionate	20	96	23.5	3.5	5	13.8
3	8 Control		—	—	16.8	3.0	5	26.5
	8 Normal	Estradiol dipropionate	2	120	17.5	3.4	5	15.1
	8 Normal	Estradiol dipropionate	10	120	22.6	3.9	5	13.6
7	13 Control		—		15.3	2.6	8	32.5
	14 Normal	Estradiol benzoate	1.3	48	14.9	2.9	8	26.2
	14 Normal	Estradiol benzoate	1.3	72	20.7	3.0	8	20.1
8	16 Control		—	—	13.8	2.3	8	24.7
	16 Normal	Estradiol benzoate	2.6	72	17.4	2.7	8	18.6
	16 Normal	Estradiol benzoate	2.6	96	15.6	2.7	8	17.4
9	13 Control		—	—	16.3	2.4	8	33.2
	14 Normal	Estradiol benzoate	1.3	72	22.6	3.2	8	21.5
11	10 Control		—	—	12.6	2.3	6	38.6
	10 Normal	Estradiol benzoate	1.3	96	16.3	2.8	6	25.5
12	10 Control		—	—	14.7	2.7	5	48.2
	8 Normal	Estrone	20	72	15.3	3.1	5	44.3
	8 Normal	Estrone	20	96	13.7	2.6	5	24.9
13	8 Normal	Estrone	10	96	19.7	3.5	5	14.4
	8 Normal	Estrone	10	120	16.8	3.3	5	14.0
16	9 Control		—	—	14.2	2.4	5	51.2
	8 Normal	Stilbestrol	20	96	18.4	3.2	5	27.9

from the endometrial biopsy. A group of women were selected who were constantly available for observation and on whom weekly endometrial biopsies and careful record of menstrual cycles could be made. Any alteration in the duration of the cycle, or character of the endometrial histology could be interpreted as changes in the ovary and presumably of the pituitary stimulation to the ovary. The gonadotrophic hormone in the urine was extracted by means of selective adsorption and assayed on immature rats.

These procedures on women were carried out as follows: women with normal cycles were given a daily administration of estrogen with a steplike increase of dosage from 1 to 30 days postmenstrually. As indicated in Fig. 6, this procedure produced an anovulatory cycle suggestive of failure of gonadotrophic stimulation of the human ovary. While similar experiments have been reported before, it is of some interest that these anovulatory cycles could be repeated in three sequential months.[2, 3]

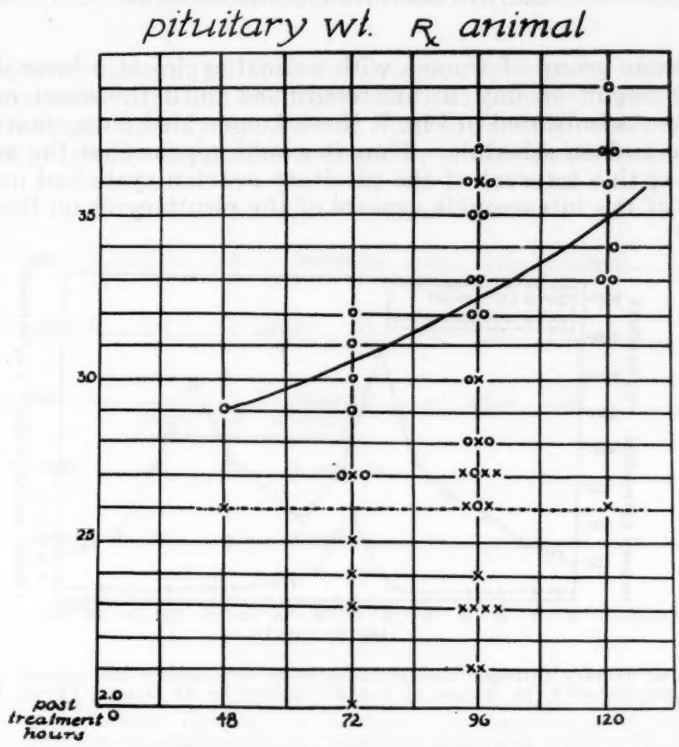

Fig. 3.—The weight of the pituitary gland increases following a single dose of estrogen at progressive intervals after the injection.

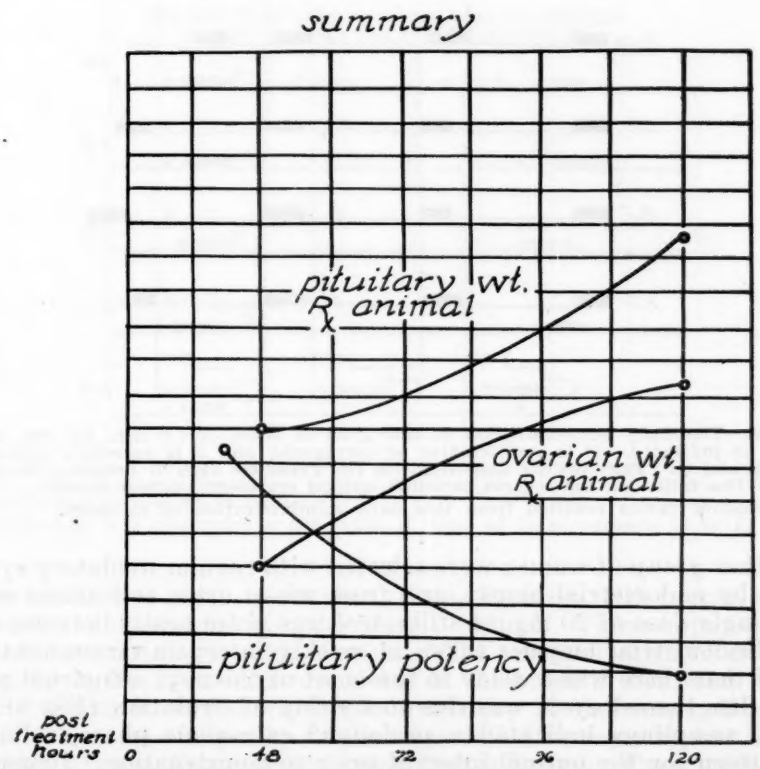

Fig. 4.—Summary of Figs. 1, 2, and 3, indicating that following estrogen administration there is a rise in pituitary weight which is accompaned by an increase in ovarian weights and a decrease in pituitary potency. These curves suggest that estrogen causes a release of pituitary gonadotrophin.

In the same group of women with normal cycles at a later date, estrogen therapy was begun on day 15 and continued until the onset of bleeding or until day 28. As indicated in Fig. 7, these women bled from a normal secretory endometrium and on schedule. Thus it would appear that the administration of estrogen at this interval of the pituitary-ovarian cycle had no influence on the activity of the luteotrophic aspects of the pituitary or on the existing corpus luteum.[3]

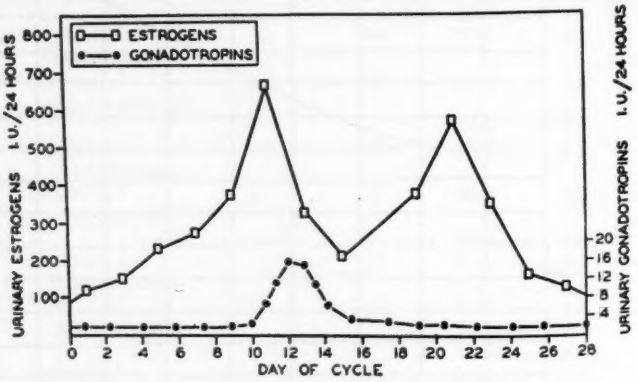

Fig. 5.—Curve of urinary estrogen and gonadotrophin throughout the normal menstrual cycle. The estrogen precedes the release of gonadotrophins by 48 hours. (From D'Amour.[9])

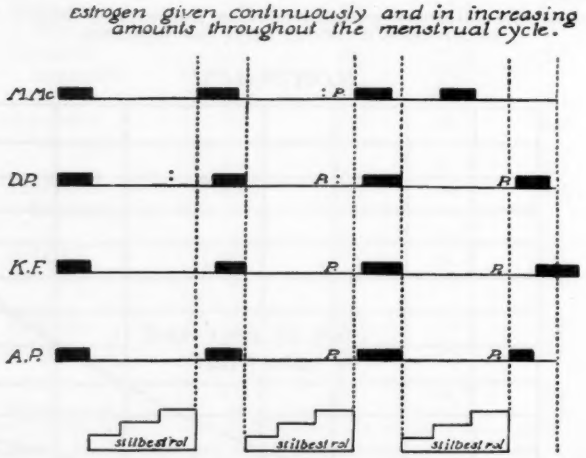

Fig. 6.—The daily administration of estrogens in doses of 1.0 mg., 2.0 mg., and 3.0 mg. was given as indicated. *P* is proliferative or estrogenic, and *S* is secretory endometrium, as obtained by biopsy. The vertical lines indicate the expected date of menses. The black bars on the base line following the several patients' initials represent vaginal bleeding.

Anovulatory cycles resulted from this daily administration of estrogen.

Another group of women were selected with regular ovulatory cycles as determined by endometrial biopsy, and from whom urine collections were possible. A single dose of 20 mg. of stilbestrol was given orally between day 5 and day 8. Endometrial biopsies taken at weekly intervals throughout the cycle indicated that there was a delay in the onset of the next menstrual period and that this lengthened cycle was due to a delay of ovulation (Fig 8). The endometrial samplings indicated a prolonged estrogenic phase, followed by a luteal pattern for the normal interval prior to menstruation. Urinary studies indicated that there was a considerable release of gonadotrophin which was recovered in the urine 48 to 96 hours after the administration of the estrogen.[4]

These experiments suggest that the gonadotrophin was released from the pituitary between the fifth and the eighth days at a time when it does not normally occur, and presumably the follicle was too immature to respond at this time. Fifteen to twenty days later, however, normal ovulation followed.

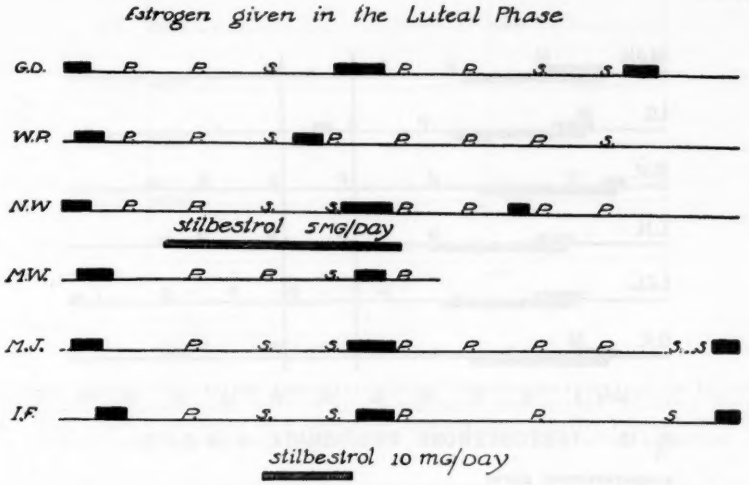

Fig. 7.—See legend, Fig. 6, for symbols. The top three patients received 5 mg. stilbestrol and the bottom three patients 10 mg., as indicated. The postovulatory administration of estrogen had no effect on the endometrial or menstrual cycle and presumably no effect on the corpus luteum or luteotrophic action of the pituitary.

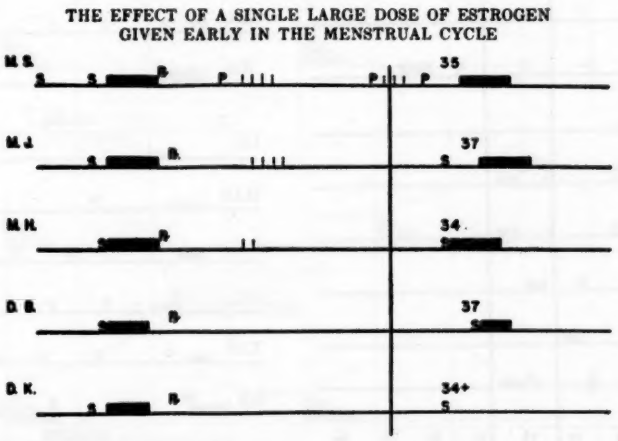

Fig. 8.—See legend, Fig. 6, for symbols. At R_x, a single dose of 20 Gm. of stilbestrol was given orally. The figures indicate the length of the treated menstrual cycles. The delay in menstruation is due to a delay in ovulation.

Gonadotrophin was recovered in the urine of some of these patients 36 to 48 hours after treatment.[4]

Testosterone was given to another group of women with normal cycles and similar weekly endometrial biopsies were obtained. These experiments were similar to those carried out with estrogen. The administration of androgen beginning early in the cycle caused a delay in the onset of ovulation and in the subsequent menstrual cycle, which was ovulatory in character. The administration of testosterone after the twelfth day failed in any way to alter the endometrial pattern or the menstrual cycle that followed. The steplike increase in testosterone beginning with the first day of the cycle produced anovulatory menstruation (Figs. 9 to 11).

Similar experiments were carried out with androstenediol in 50 mg. doses and, as indicated in Table II, no significant alterations in the endometrial pattern or the menstrual cycles could be noted from these experiments. Presumably, therefore, in these doses this substance has no effect upon the pituitary-ovarian cycle.

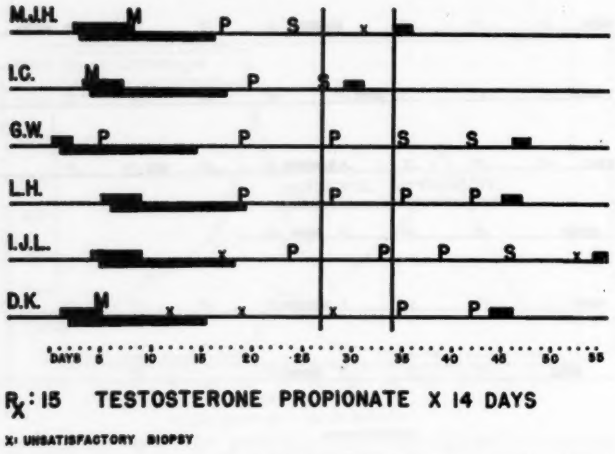

Fig. 9.—See legend, Fig. 6, for symbols. Testosterone was given intramuscularly in 15 mg. doses beginning during the menstrual phase as indicated by bar under the patient's base line. Ovulation was delayed, but ensued in a normal fashion 10 to 20 days later.

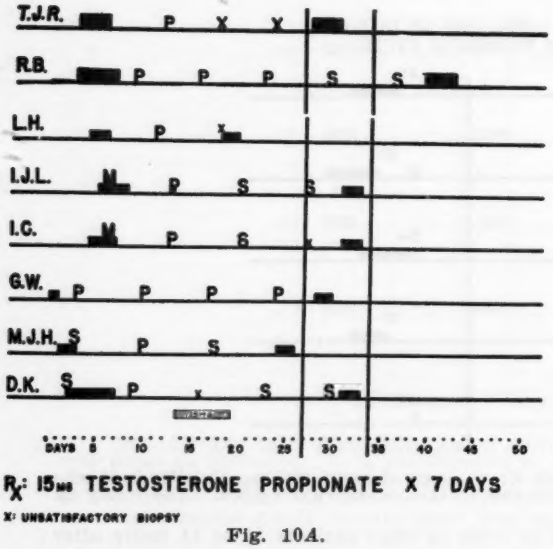

Fig. 10A.

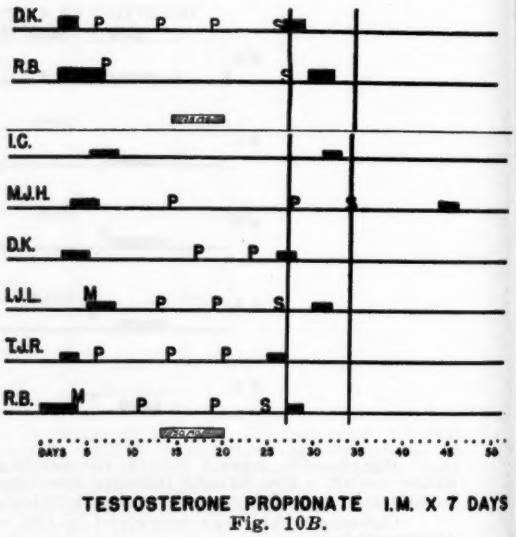

Fig. 10B.

Figs. 10A and 10B.—See legend, Fig. 6, for symbols. Testosterone was given intramuscularly in doses of 15 mg., 25 mg., and 50 mg. as indicated in the postovulatory phase. No consistent alterations in menstrual or endometrial cycles were observed.

In summary, these experimental data indicate that in the woman a single administration of estrogen early in the menstrual cycle (prior to ovulation) causes a delay in ovulation which is temporary and is followed by a normal ovulatory pattern in the current and subsequent menstrual cycles. This delay in ovulation is associated with a premature release of gonadotrophic hormone in the urine. It is further apparent that if the estrogen is administered after ovulation has occurred and the pituitary has released its gonadotrophic hormone,

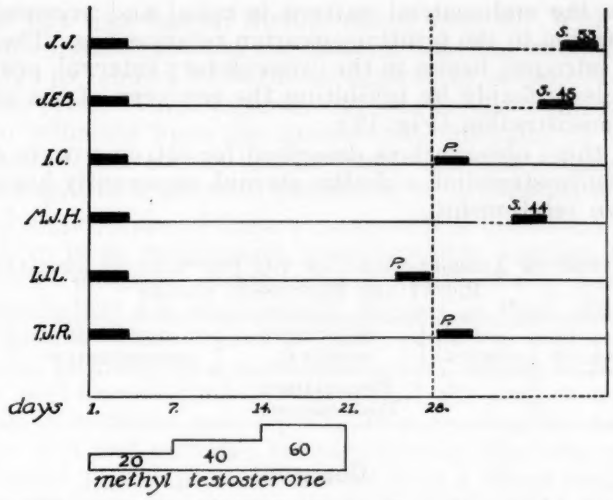

Fig. 11.—See legend, Fig. 6, for symbols. Methyl testosterone was given by mouth as indicated. Ovulation was suppressed in 3 of the 6 patients, which was followed by anovulatory menstruation. The other 3 patients had complete amenorrhea for the treated cycle, which was followed by a normal ovulatory cycle approximately 20 to 30 days after cessation of androgen treatment.

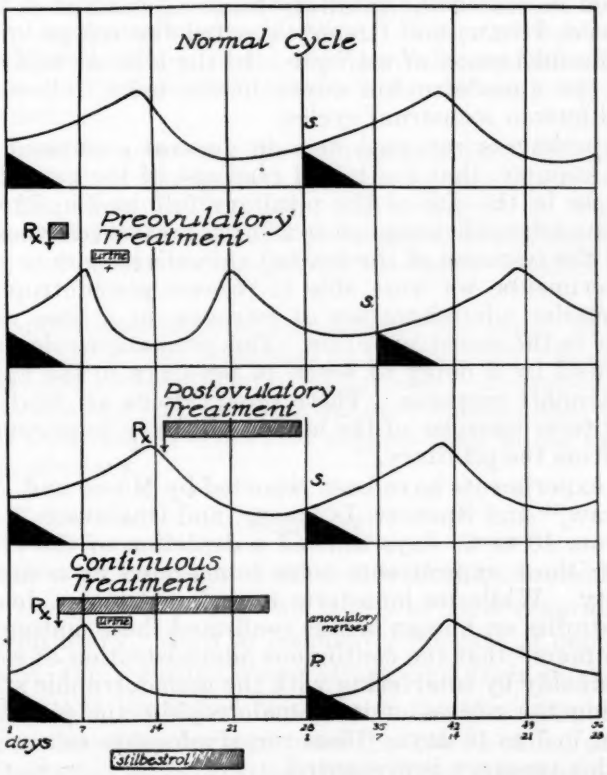

Fig. 12.—Schematic summarization of the effect of estrogen (and/or testosterone) on the pituitary. Top chart indicates the gonadotrophin curve in a normal cycle.

When estrogen is given before ovulation for a short interval, the pituitary is stimulated to release its hormone which appears in the urine. The pituitary recovers in 7 to 10 days and ovulation and menstruation follow.

If estrogen is given post ovulation, no effect is noted.

If estrogen is begun early and continued, the pituitary is stimulated to release its hormone and remains depleted until estrogen is discontinued. The bleeding which follows is anovulatory. The pituitary then recovers and the following cycle is normal.

no alteration in the endometrial pattern is noted and presumably, therefore, there is no alteration in the pituitary-ovarian relationship. The continuous administration of estrogen, begun in the preovulatory interval, prevents ovulation during that cycle probably by inhibiting the recovery of the pituitary during the estrogen administration (Fig. 12).

In general, these observations described for estrogen were also found with testosterone. Androstenediol, a similar steroid, apparently has no effect on the pituitary-ovarian relationship.

TABLE II. THE EFFECT OF ANDROSTENEDIOL ON THE PITUITARY AS REVEALED IN ENDOMETRIAL BIOPSY AND MENSTRUAL CYCLES

DOSE MG.	NO. OF PATIENTS	TREATMENT INTERVAL	OVULATION (ENDOMETRIUM)	MENSES
50	5	Preovulatory	+	Normal
50	5	Postovulatory	+	Normal

Comment

These groups of experiments taken individually provide a confusing picture. Many of these observations have been reported singly by various investigators. The increase in pituitary weight following a small dose of estrogen was reported by Baker and Everett.[5] Burch and Cunningham,[6] reported that small doses of estrogen increased the pituitary-hormone content of treated animals. Lane,[7] and Fevold, Hisaw, and Greep[8] reported the release of gonadotrophin following the administration of estrogen. In the clinical field, D'Amour[9] demonstrated that the gonadotrophin curve in the urine followed the estrogen curve in normal human menstrual cycles.

The rat experiments reported here in general confirmed the findings of these observers, namely, that the initial response of the rat pituitary to estrogen is an increase in the size of the pituitary followed in 72 to 120 hours by release of its gonadotrophic-hormone content as measured by assay of the pituitary gland, and the response of the treated animal's ovaries to such release. In the human experiments, we were able to recover gonadotrophin in the urine following the similar administration of estrogen, at a time when it does not normally appear in the menstrual cycle. This premature release of the gonadotrophin is followed by a delay of seven to ten days in the appearance of the normal gonadotrophic response. These observations all tend to suggest that the initial short-term response of the human pituitary to estrogen is the release of its hormone from the pituitary.

Long-term experiments have been reported by Moore and Price,[10] Leonard, Meyer, and Hisaw,[11] and Spencer, D'Amour, and Gustavson,[12] which over periods ranging from 10 to 60 days showed a depletion of the pituitary gonadotrophic content; these experiments were interpreted as a suppression of the pituitary activity. While no long-term experiments were done on the rat in this series, the studies on human beings confirmed those findings of Sturgis and Albright,[2] and others,[3] that the continuous administration of estrogen prevents ovulation, presumably by interfering with the gonadotrophic stimulation of the ovary. Following the release of its gonadotrophin, the pituitary recovers its hormone content in 7 to 10 days. However, if adequate estrogen concentration is maintained, this recovery is prevented.

The early administration of estrogen causes a premature release of gonadotrophin and its continuance prevents the recovery and subsequent ovulation, resulting in an anovulatory cycle.

Several possible interpretations are available on the effect of late (postovulatory) administration of estrogen. The most likely is that the pituitary depletes itself of its gonadotrophic hormone content in the process of ovulation,

and estrogen at this time has no further effect upon it. With the discontinuance of estrogen administration at the onset of bleeding, the pituitary has from seven to ten days to rebuild its hormone content in preparation for ovulation in the succeeding cycle. These experiments give further evidence that estrogen has little or no influence upon the luteotrophic hormone of the pituitary or upon the life span of the corpus luteum itself, and cast considerable doubt on the value of estrogen in hypoluteal states and in threatened abortion.

The clinical significance of these experiments is somewhat limited. At the present time there is no satisfactory gonadotrophic complex for clinical use. The several animal pituitary gland extracts are relatively potent, but due to antihormone production are considerably limited in their clinical usefulness. It seems quite possible that estrogen properly employed may serve as a method of stimulating the pituitary to a more satisfactory release of its gonadotrophic hormone. The well-known clinical response of the patient with anovulatory uterine bleeding to artificial cycles probably represents the salutary effect of cylic stimulation and rest provided the pituitary by this form of estrogen therapy. Thus it would appear possible that we have a direct method of stimulating the human pituitary to a more satisfactory release of the gonadotrophic hormone complex.

Clinical use of these observations is also potentially valuable in anovulatory sterility. All of us, I am sure, have seen patients who have conceived either during or immediately following the exhibition of artificial cycles in an attempt to control irregular uterine bleeding. Weisman[13] has recently reported a series of this nature in which 18 out of 27 anovulatory, infertile women, as determined by endometrial biopsies, obtained a secretory endometrium and 12 subsequently conceived.

It is of interest to observe that androgens follow an essentially similar pattern. While complete studies have not been carried out, they are sufficiently adequate to confirm those findings seen with estrogen. It is possible that the effective dosage of androgen might be more useful in the control of functional uterine bleeding and presumably might have a similar beneficial effect upon the pituitary.

In recent months there has been considerable discussion and several reports dealing with the effect of androstenediol on the pituitary. It has been reported to be a nonandrogenic steroid useful for pituitary suppression. Studies conducted in this laboratory but not reported here indicate that it is indeed nonandrogenic, and these experiments also suggest that, in the doses used, it has no effect on the pituitary.

Summary

These diverse experiments, in corelation with those found in the literature, tend to resolve the conflict in the two points of view regarding the effect of estrogen on the pituitary. As is so frequently the case, it depends on the plan of the experiment, the recorded observations, and their interpretation. It is our interpretation that the initial response of the pituitary to estrogen is the release of the gonadotrophic hormone, and that the so-called suppression effect is in reality a depletion or exhaustion effect. These studies suggest that continued estrogen administration prevents the recovery of the pituitary and this response has been called a depression. It appears to us important to recognize this biphasic response of the pituitary to estrogen, and the potential clinical advantage which this information may provide the physician in the management of anovulation.

Conclusions

In summary the following conclusions seemed to be warranted from these experiments:

1. The probable initial effect of estrogen on the pituitary is to stimulate a release of the gonadotrophic hormone.

2. The pituitary apparently recovers its gonadotrophic hormone content in from seven to ten days.

3. The continued administration of estrogen prevents this recovery of gonadotrophic hormone.

4. Androgens apparently affect the pituitary in a manner similar to estrogens.

5. Androstenediol as used had no demonstrable effect on the pituitary-ovarian cycle.

6. This method of enhancing the pituitary gonadotrophin has shown some promise on clinical trial. It is hoped that others will be stimulated by this report to make clinical observations on the usefulness of these experimental data.

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Discussion

DR. WILLARD M. ALLEN, St. Louis, Mo.—This paper adds another solid stepping-stone to the path that will eventually lead us to a full understanding of the menstrual cycle. The authors have already shown by actual experiment that chorionic gonadotrophin is the hormone which will keep the corpus luteum functioning beyond its normal life span of two weeks. That experiment provides the first proof that the placental gonadotrophin really does keep the human corpus luteum functioning during the early weeks of pregnancy. They have also shown that the endometrium can be kept functional after the corpus luteum has regressed by the administration of the proper doses of estrogen and progesterone, whereas neither hormone by itself will prevent the onset of menstruation at the expected time. These experiments suggest, of course, that chorionic gonadotrophin causes the ovary to produce both estrogen and progesterone, provided there is a functional corpus luteum already in the ovary. Now they have turned their attention to another aspect of the cycle, trying to find out whether estrogen has any effect on the mechanism of ovulation.

The experiments in animals show again that the effect on the pituitary is dependent upon the duration of administration. They have shown that a single dose of estrogen enhances the activity of the pituitary for two or three days following which there is a falling off of activity. The effects in the human being presumably are similar since there was an increase in the gonadotrophin in the urine followng a single fairly large dose of stilbestrol. These observations deserve special emphasis since it is so well known that the absence of estrogen, produced by castration, irradiation, or simple aging, also causes an increase in the activity of FSH. Some

explaining is required to reconcile such completely opposite effects, yet the facts seem well established. The authors have carefully avoided any speculation that might reconcile these peculiar phenomena. They are content to point out the possible usefulness of the observation that estrogen does stimulate the production of gonadotrophin.

There remains one further aspect of the study which again points out how little we really know regarding the actual phenomena that lead to that final spurt on the growth of the follicle and the shedding of a mature, fertilizable ovum. Under normal circumstances there is a slow steady growth of the follicle followed by rapid increase in the size of the follicle, change in the appearance of the granulosa, production of the first polar body, and ovulation. This is what goes on just before ovulation. The administration of estrogen between the fifth and eighth days caused an increased production of gonadotrophin but it did not bring about ovulation. In fact, quite the opposite. Ovulation was delayed until the pituitary or ovary or both had recovered from the hormone insult. Yet after recovery the ovary presumably ovulated normally and contained a functional corpus. Now the question is, "Why did not the induced burst in pituitary activity lead to early ovulation?" Was it because the ovary was not ready for stimulation or was it because the stimulus was not the proper stimulus? My guess is that the stimulus was not the proper one. Certainly an ovary is capable of ovulating at least a week earlier than in most cycles for how else can we explain 21-day ovulatory cycles? We might say that there was too much of a stimulus but that seems unlikely. In animals such as the rabbit the number of eggs shed at ovulation bears a fair relation to the amount of chorionic gonadotrophin injected—large doses many eggs, small doses only one or two eggs. If we are to conclude that ovulation did occur because the maturest follicle on the eighth day was too immature to respond to the stimulus we must admit defeat in this type of experimental subject. Giving the estrogen a little later in the cycle might accelerate ovulation but the time relations are such that it would be virtually impossible to prove that ovulation occurred because of the stimulus provided by the estrogen.

In the interrelations which must exist between the pituitary and ovary there must be some reciprocal relationship where one hormone inhibits another. It has been virtually axiomatic that too little estrogen results in pituitary overproduction (menopause, high FSH) and too much estrogen in low pituitary activity (suppression of ovulation by overdosage with estrogen). May it not be, however, that there is a synergism between estrogen and FSH up to a certain point? At any rate this highly stimulating paper gives us some new ideas to work with.

I am wondering too whether it is not possible to study the estrogen-induced pituitary hyperactivity in greater detail. Is the gonadotrophin produced FSH, LH, or both? A test developed some years ago by Witschi (Proc. Soc. Exper. Biol. & Med. 35: 484, 1936) called the Weaver Finch test seems to be specific for LH. In this test the LH induces a black bar on certain sex-specific feathers of the African finch, whereas FSH, thyrotropic, adrenotropic, and growth hormones are without effect. Utilization of this test might unravel some of the effects observed with estrogen.

DR. DAVID N. BARROWS, Philadelphia, Pa.—This experimental work done by Dr. Brown has helped to clarify a field of intense theorization in which clinical usage is still in the stage of infancy. Such men as Zondek, D'Amour, Hohlweg, and Halpern, and too many others to mention have engaged in experimental research in this problem. However, in the human being, the study of the effects of the estrogens and other steroids on the anterior pituitary gland has been restricted because of the nature of the gland, the inability to secure pure end-products of its activity, or the exact nature of its secretions. It seems established that estrogens produced in the ovary are formed by the granulosal and to a lesser extent by the luteal cells. Estrogen administration in the second half of the cycle will have no physiological effect on menstruation unless the dosage is such as to produce a complete suppression of the next period. Small doses may even enhance the action of the progesterone and thus produce an increased vascularity of the decidua theoretically better adapted to the implantation of pregnancy.

With the continuous administration of estrogen during the full thirty days of a menstrual cycle, ovulation is suppressed. These changes can be repeated through several suc-

cessive cycles. This principle was applied to one of my private cases. Using increasing doses of stilbestrol for the treatment of clinical endometriosis as proposed by others, I was able, over a period of months to keep a 32-year-old gravida iii, para iii, amenorrheic with doses of the drug reaching as high as 125 mg. per day. Of course at the beginning the dosage was smaller and each time the patient started to spot as a tolerance to the dosage of stilbestrol was reached, the daily dose was increased. After a period of 6 months suggestive symptoms of pregnancy were noted, and after nine months of this treatment a diagnosis of pregnancy was clinically made. Shortly thereafter, the patient started to bleed, developed cramps, and finally aborted. The increasing doses of stilbestrol suppressed the action of the pituitary gonadotrophins, and yet this woman was able to conceive. The effect was beneficial on the clinical endometriosis because the uterosacral ligaments, which had previously shown involvement, were now clear and the dysmenorrhea has disappeared.

It has been suggested by D'Amour and his associates that a rise in the chorionic gonadotrophic hormone excretion occurs between the twelfth and sixteenth days before the next menstrual flow. If sufficient estrogen is administered or if the estrogen content of the blood in the first half of the cycle is high, thus delaying ovulation and exhausting the available gonadotrophin, ovulation with an ensuing pregnancy cannot take place because of the fact that the chorionic gonadotrophic hormone maintains the corpus luteum. In some of our cases of frequent early abortion this seems to have been an important factor which I have overcome by the administration of chorionic gonadotrophic hormone through the fourth month. One must be careful of reactions because certain anterior pituitary extracts antagonize the gonadotrophic action of subcutaneously administered gonadotrophic extracts. This effect has been attributed to the presence in the anterior lobe of an antagonistic hormone which causes follicular atresia and inhibits the action of the gonadotrophins.

I have also found this form of therapy to be of use in the cases of so-called pseudosterility where menses were either regular or slightly delayed but where no demonstrable pregnancies took place. Whether it is the chorionic factor alone or the fact that there is an excess of estrogen-stimulating factors in these individuals, I cannot tell you, but I can say that the end result justifies the treatment. In the last two years, I have had at least a half dozen cases of this type all of which went to term and delivery.

To demonstrate what I mean, I will present the case of Mrs. B. J., a 22-year-old white woman, who consulted me because of sterility. The general physical examination was negative except for a thickness across the lower abdomen and wide hips. She was about 5 feet, 2 inches, in height and weighed 132 pounds. The periods were slightly irregular, and the thyroid normal as determined by the basal metabolic rate, the tubes were patent on Lipiodol study, and the endometrium on biopsy showed no secretory phase. The husband's sperm count was normal. The diagnosis was ovarian-pituitary imbalance. Systematic biweekly injection therapy was started, using 500 I.U. of chorionic gonadotrophic hormone, in July, 1949. By October, the periods were of normal duration and the weight had dropped to 121 pounds and the saddle bags had disappeared from the abdomen and hips. This treatment was continued and the expected period due on October 10 was missed. On October 21 a slight staining took place but after the administration of progesterone this too disappeared and when pelvic examination was performed on November 23, she was found to be pregnant. An Aschheim-Zondek test confirmed this diagnosis. The biweekly injections were continued until February when it was determined that the pregnancy was of at least four full months' duration. At the expected time this girl had a normal spontaneous delivery without complications. It is interesting to note that there are three sisters in this family all with the same difficulty, and so far I have been successful on obtaining pregnancies for two. The third has a husband with a low sperm count.

DR. E. C. HUGHES, Syracuse, N. Y.—If estrogen is given over any prolonged period of time, as Dr. Brown has shown, anovulatory cycles will occur and eventually hyperplasia of the endometrium will result. If estrogen is given after ovulation, nothing will occur. However, if it is given prior to ovulation and the dose is carefully regulated, stimulation of the pituitary will be effected. Three years ago I reported here a series of 12 patients who

had been given tiny doses of diethylstilbestrol, namely 0.1 mg. for 12 days in the preovulatory time. Following this therapy, the total gonadotrophins were increased and the endometrial biopsies were improved. Since that time we have had considerably more cases which have shown similar effects. It seems to me that the size of the dose and the time of administration are extremely important. I would like to ask Dr. Brown if the natural estrogen has the same effect as the diethylstilbestrol which he used in his series.

DR. BROWN (Closing).—Dr. Hughes' question as to the choice of natural or synthetic estrogens is of interest. I believe we can use them more or less interchangeably, for in all probability it is only a matter of dosage or dose equivalents. However, I do not have the necessary experimental information to answer that point specifically.

The question of Dr. Willard Allen as to whether we have any information regarding the presence of luteotrophic hormone in the urinary extract of gonadotrophin is important, but unfortunately we do not have information on that point. We were not able to prepare enough material from the 24-hour urine specimen to make such an assay feasible.

Dr. Hughes' point regarding the proper timing of estrogen is of utmost clinical importance. May we emphasize that this is entirely an experimental report? We were trying to learn what estrogen does to the pituitary gonadotrophin. We quite agree with Dr. Allen that in the clinical application of these experimental observations, the estrogens should be given when the follicle is mature, where an augmentation of the gonadotrophin release might favorably effect ovulation and luteinization. I trust that some of you will give these suggestions a clinical trial and let us know whether we are on the right track.

THE CLINICAL SIGNIFICANCE OF MISPLACED ENDOCERVICAL TISSUE—HETEROPLASTIC ENDOCERVICAL TISSUE*

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(From the Department of Obstetrics and Gynecology of Jefferson Medical College and Methodist Hospital)

CARCINOMA of the cervix of the uterus is one of the most common forms of malignancy occurring in women. Since the part of the cervix most often involved with the lesion can easily be examined, it will be the purpose of this presentation to introduce a standard for the evaluation of the normal cervix and to discuss what we have chosen to call misplaced endocervical tissue or heteroplastic endocervical tissue. It is a generally accepted fact in clinical work that malignancy seldom develops in normal tissue, and for that reason it should be the aim of all clinicians to have an acceptable standard for the evaluation of the normal cervix.

Premarital examinations and the willingness of women to submit to pelvic examination in the last few decades have given the physician an opportunity to observe more carefully the female genitals and to form conclusions which do not coincide with ideas that have been expressed by many of the earlier investigators.

Adair[1] in 1910 reviewed carefully the theories of Fischel, Ruge and Viet, Gottschalk, and Robert Meyer which were discussed before the Berlin Gynecological Society in February, 1909, and it is the views expressed in Adair's presentation which have influenced the thinking and teaching on the behavior of cervical epithelium.

Although this presentation may seem elementary, it is our thought that much confusion exists in the minds of physicians and teachers as to the significance of so-called erosion and eversion of the cervix.

The views expressed in this presentation are based on the interest and experience of more than 25 years and it includes the observation and management of many hundreds of patients with so-called erosion or eversion of the cervix. The clinical findings in many instances have been correlated with routine histological studies of tissue taken from the involved portion of the cervix with the idea of studying the behavior of the columnar and squamous epithelium.

The clinical material utilized for this presentation can be itemized as 400 unselected case histories which represent a spot check of many hundreds of patients. Two hundred of these patients were virgins or nulliparous women in the second or third decade of life, who presented themselves for premarital examination or a gynecological check-up or who desired an examination because of a vaginal discharge.

The other 200 patients were women who were treated for cervical eversion or erosion and who subsequently became pregnant and were delivered.

*Presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

Definition

The term heteroplastic endocervical tissue seems to describe adequately and accurately the phenomenon of misplaced endocervical tissue as it appears on the vaginal portion of the cervix during the reproductive period in women. We have assumed by this term that the misplaced endocervical tissue as observed during the reproductive period is congenital in origin and that it is the formation of normal endocervical tissue in an abnormal position. It is actually only recognizable after puberty and this developmental change which takes place at puberty exists with changes throughout the reproductive period of the woman if it is not destroyed. Cervicitis, endocervicitis, granular and papillary erosions, etc., are actually variable degrees of changes which may take place in what was originally misplaced normal endocervical tissue or heteroplastic endocervical tissue.

Anatomy and Physiology

The following description of the uterine cervix during the normal procreative period is our concept of a normal cervix. It is a complex structure which is a component part of the vagina and the uterus, and it serves as a structure to which are attached the important supports of the uterus. Its contour is evenly cylindrical with its central portion elevated into a gentle curve.

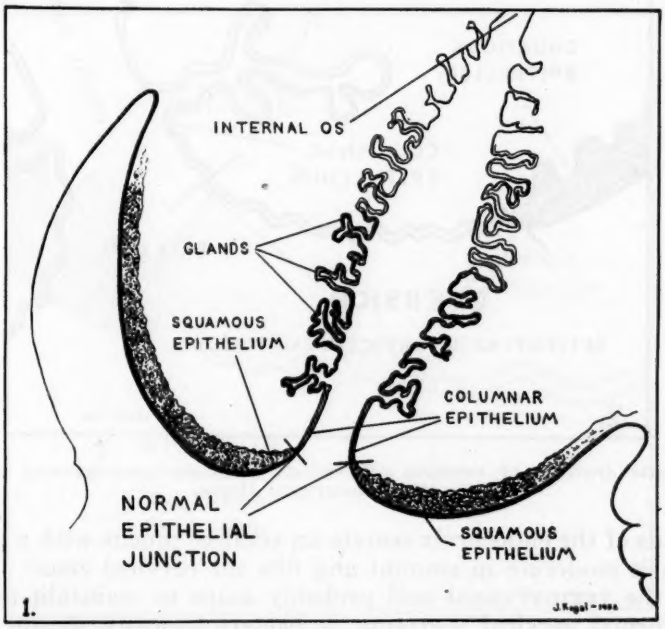

Fig. 1.—Schematic drawing of a normal cervix. Normal epithelial junction about 1 mm. above surface plane of the portio.

The size of the adult cervix varies slightly regardless of parity. It measures from 2.0 to 3.0 cm. in its largest diameter and is slightly larger at the base than at the apex. The mucosa of the cervix exhibits considerable hyperplasia and perhaps metaplasia during pregnancy and, although the interstitial part of the cervix is fibromuscular, it undergoes very slight evolutionary changes in pregnancy.

The endocervical mucosa extends from the border of the endometrium at the internal os of the cervix to a point of juncture with the squamous epithelium

of the vagina. It is thrown into folds which present a large surface with a definite type of columnar epithelium and a number of compound racemose glands which extend for a depth of 1 or 2 mm. into the interstitial portion of the cervix and it possesses a definite basement membrane.

The external os of the cervix in the nulliparous female is a circular structure about 3 mm. in transverse diameter and quite regular in outline. Its circumference marks the area where the constriction of the interstitial portion of the cervix develops and is 0.5 mm. inside the surface plane of the tip of the portio. The size and shape of the external os of the cervix may be altered by such factors as labor, trauma, infections, inflammatory reactions, and congenital malformations. The cervical canal is a straight tubular structure with parallel walls and no areas of constriction or dilation. Wollner[2] thinks that the endocervical epithelium undergoes cyclic changes during the menstrual cycle which are as definite as those observed in the endometrium.

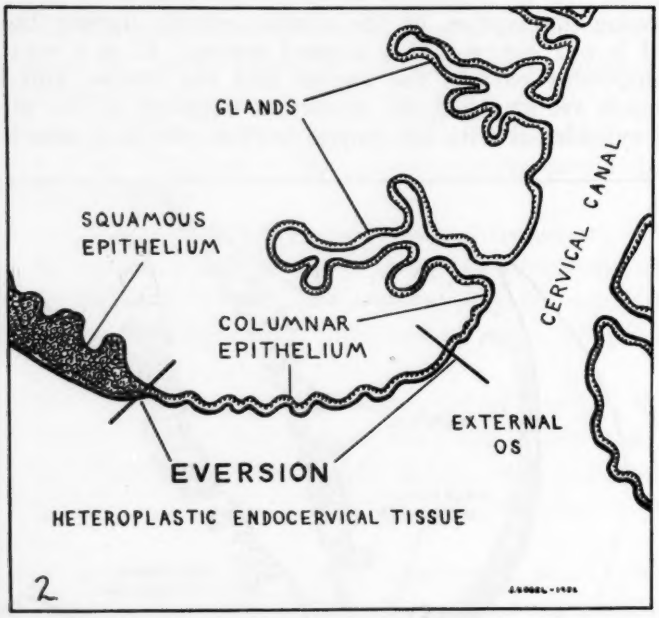

Fig. 2.—Schematic drawing of eversion of cervix. Misplaced endocervical tissue or heteroplastic endocervical tissue.

The glands of the endocervix secrete an alkaline mucus with a pH of 9.2.[3, 4, 5] The secretion is moderate in amount and fills the cervical canal. Some of it is deposited in the vaginal canal and probably helps to maintain normal vaginal moisture. Normal cervical secretion is bacteriologically sterile and contains desquamated epithelium and some mucus cells and glycogen; the amount and viscosity vary during the menstrual cycle.

The Portio Vaginalis

The portio vaginalis of the cervix is covered with a membrane contiguous with the vagina, is smooth and light pink in color, and is lightly attached to the body of the cervix, and on palpation gives a sensation of pliability, nonfixation, and regularity in texture.

The portio of the cervix is constantly bathed in vaginal secretion which has a normal acid reaction with a pH near 4.5 and it is apparent that the

squamous epithelium which covers the portio is adjusted to this acidity since alterations in vaginal acidity cause obvious changes in the appearance of the vaginal membrane. We have outlined somewhat didactically our standards for a normal cervix,[6] which are hypothetical but fundamental. If deviations from these standards occur, they should be considered abnormal and proper means for their study and correction should be instituted.

Heteroplastic Endocervical Tissue

We think that much confusion exists as to the significance of heteroplastic endocervical tissue. It would appear that this particular phenomenon is often accepted as insignificant since its occurrence is so frequent. It occurred in 53 per cent of the patients observed by us. It represents the formation of abnormal or normal endocervical tissue in an abnormal position and is contiguous with the mucosa of the endocervical canal. Consideration as to the significance or potentiality of this phenomenon for serious organic disease has not been sufficiently emphasized. The lack of emphasis exists for the reason that during a complete genital examination some heteroplastic endocervical tissue will have been observed in many individuals and unless understanding and skill have been exercised, considerable difficulty will have been experienced in destroying completely and successfully the heteroplastic tissue.

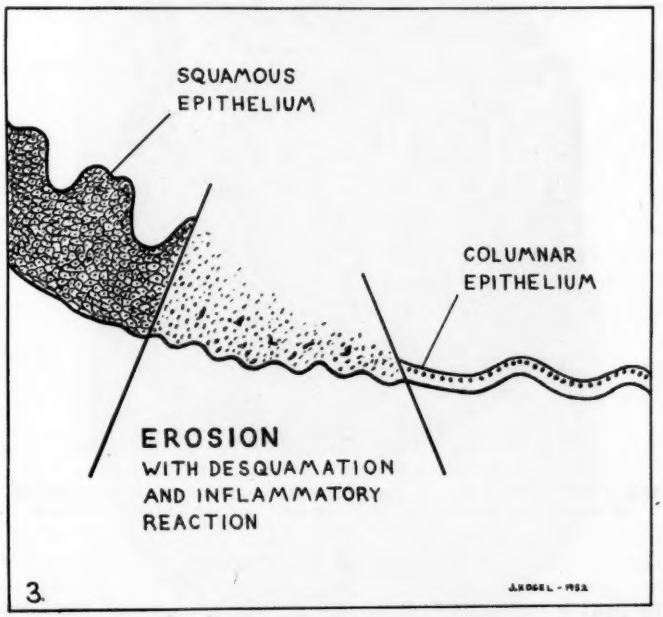

Fig. 3.—Schematic drawing of erosion of cervix with desquamation of columnar epithelium and inflammatory reaction.

Heteroplastic endocervical tissue functions as normal endocervical tissue originally, and is histologically identical with it, and is adapted physiologically to the habitat of its own alkaline secretion. However, it is exposed to the acid vaginal secretion which is an abnormal habitat for it. This habitat is probably responsible for the unusual behavior of the misplaced columnar epithelium. Erosions and inflammatory reactions occur at the site where the squamous epithelium and the columnar epithelium meet. If this condition is allowed to continue, it will often involve all of the misplaced columnar epithelium to various degrees.

Eversions of the Cervix

Eversion of the cervix is described as a turning outward of the cervical canal (Fig. 2). Eversions are actually areas of heteroplastic endocervical tissue which are in most instances congenital in origin. These formations, however, are not obvious until the genitals are mature. This conclusion is proved in our own experience by the frequency with which we have observed cervices with heteroplastic endocervical tissue in nulliparous and virginal women (53 per cent). This is further proved in our experience by the observation that eversions of the cervix rarely have recurred following treatment, when the delivery was normal. Two hundred nulliparous and virginal women with congenital eversion of the cervix have been treated by destroying the heteroplastic endocervical tissue. The histories of these women have been reviewed following labors and deliveries and in only 3 per cent did the eversion or erosion recur. These recurrences could be attributed to traumatic labor or delivery or inadequacy of the original treatment. We have learned from these data that congenital eversions are frequent and when destroyed properly do not recur.

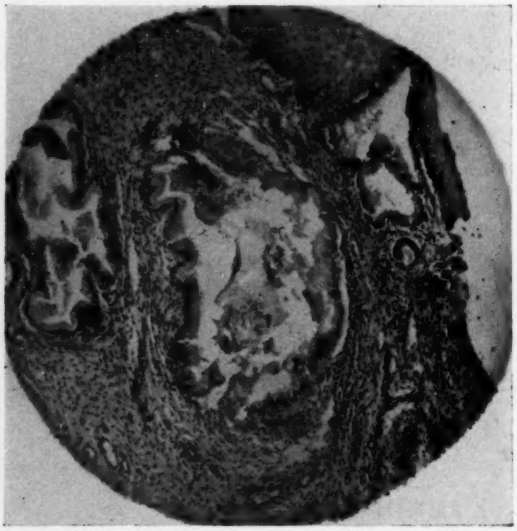

Fig. 4.—Tissue taken from juncture of squamous and columnar epithelium on portio. Absence of surface columnar epithelium and inflammatory reaction.

Erosion of the Cervix

It appears that a cervical erosion (Fig. 3) is a loss of surface epithelium at the site where the heteroplastic endocervical tissue exists and probably begins at the juncture of the two types of epithelium. It can also be demonstrated histologically by the loss of surface tissue and the inflammatory reaction which occurs at the site where the heteroplastic tissue exists.

If eversions and erosions remain untreated there are various changes which follow, such as endocervicitis with its associated stenosis, hypertrophy, formation of simple Nabothian cysts, and cystic degeneration. Granular and papillary erosions are various degrees of the degenerative or inflammatory process.

All cervices can be restored to a hypothetically normal condition if treated early, by the destruction of the heteroplastic endocervical tissue. The method used is not pertinent to this presentation.

It is only by the keen appreciation of what constitutes a normal cervix and the proper treatment of the minor changes that future cervical disease of major importance may be avoided.

Fig. 5.—Juncture of squamous and columnar epithelium shows inflammatory reaction. Surface squamous and columnar epithelium.

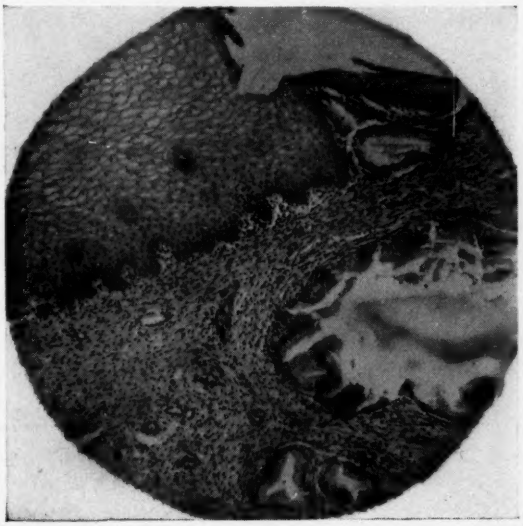

Fig. 6.—Juncture of squamous and columnar epithelium. Slight inflammatory reaction. Instability of both squamous and columnar epithelium.

It is our conviction that all areas of heteroplastic endocervical tissue should be properly and effectually destroyed. If abnormal cervices are allowed to remain untreated, extensive inflammatory changes and perhaps malignancy may develop. Certainly malignancies seldom develop in what we have described as a normal cervix.

The assumption that a cervix is normal when heteroplastic endocervical tissue is present, because it causes no serious symptoms, is fallacious.

Summary

Since carcinoma of the cervix is common, its prevention should be the goal in the management of simple diseases of the cervix. This presentation has emphasized the clinical significance of misplaced endocervical tissue or what we have chosen to call heteroplastic endocervical tissue.

Our data indicated that 53 per cent of nulliparous and virginal women who consulted us had various degrees of heteroplastic endocervical tissue. It also showed that if the heteroplastic tissue was destroyed properly it would recur in only 3 per cent of women following labor and delivery.

We have described a standard for a normal cervix.

It is our conviction that the various changes which occur in heteroplastic endocervical tissue, if allowed to persist, are caused by its existence in the abnormal habitat of the vagina. If this tissue is destroyed completely and properly it will not recur and the cervix will remain normal.

I wish to express my appreciation to Dr. George A. Hahn and Dr. Joseph F. McCloskey for their interest and suggestions in the preparation of this presentation.

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Discussion

DR. FRANK L. MC PHAIL, Great Falls, Mont.—The purpose of Dr. Mohler's paper is to introduce a standard for the evaluation of the normal cervix, to discuss misplaced endocervical tissue, and to urge that such tissue be destroyed. He believes that misplaced endocervical tissue, assumed to be congenital in origin, may be responsible for more serious cervical disease. Assuming a well-accepted fact, that malignancy rarely develops in normal tissue, the recognition of cervical pathology, combined with prompt treatment, is stressed as part of a program for the prevention of cancer of the cervix.

Whatever theory proves to be correct in regard to the etiology of misplaced endocervical tissue, this is a timely paper as our attention is directed, most emphatically, to a lesion on the cervix which is frequently considered to be insignificant. It has been our experience that, regardless of etiology, adequate diagnosis is most important in the consideration of cervical lesions. This point is of great significance if we are to dissipate some of the confusion that exists in regard to cervical lesions, particularly those which appear to be minor.

In our clinic we have little faith in punch biopsies taken from selected portions of a cervical lesion, nor in the effect of heat in the destruction of questionable cells. One case serves to illustrate the point. A woman had a lesion diagnosed as an erosion. This had been treated by topical applications for some months. A punch biopsy was then taken. This showed only an erosion. The cervix was then cauterized, in what appeared to be an adequate manner. A short time later we took an excision biopsy. Using the multiple section method, cervical erosion, metaplasia, and carcinoma in situ were found in different sections.

We find that it is possible to remove the entire squamocolumnar junction with some adjacent tissue, so that erosions or eversions are included, by taking a shallow knife biopsy. These cervices seem to heal well and appear to be normal after a few weeks. The tissue is then prepared so that the entire junctional area, the cells adjacent to it, and a reasonable amount of deeper cervical tissue are included in each section according to the method of

Hildebrand. Sections are made so that a sample is taken at least every 1.5 mm. all around the cervix. As a result approximately forty sections of each cervix are studied. Using this method we have had a sufficient number of carcinomas detected to justify our opinion that careful study of the entire tissue is most important. The only completely safe method is to make serial sections of the entire biopsy. Such detailed study is in general not economically possible without subsidy.

There are several points in Dr. Mohler's paper which deserve re-emphasis. First, a standard for the evaluation of the normal cervix is essential. Second, much confusion exists in the minds of physicians and teachers as to the significance of erosions and eversions of the cervix. As a result of this confusion, potentially serious lesions are frequently ignored or treated inadequately. Third, it is possible to dispel some confusion by stressing the importance of ruling out cancer. Dr. Mohler has stated in an earlier publication: "These procedures should never be accomplished without careful study to exclude malignancy." Fourth, it is possible that many cancers can be prevented if these lesions are destroyed.

It seems wiser to restore the cervix to normal by actual removal of the lesion, rather than by destruction. I would like to urge that abnormal tissue be removed, rather than destroyed, and that the entire tissue be subjected to careful study. Such a study would make it possible to treat cancer of the cervix in its earliest stage.

DR. RICHARD PADDOCK, St. Louis, Mo.—From the title of this paper one might assume that misplaced endocervical tissue was something akin to endometriosis. After hearing this presentation one sees the significance of endocervical tissue outside of the cervical canal proper.

In the developmental stage of the cervix, the cervical canal, up to five or six months of intrauterine life, is usually lined with squamous epithelium. The columnar epithelium of the canal develops as fetal development progresses. The misplaced endocervical tissue at the os, presenting the picture of eversion, erosion, or both, is either congenital or acquired.

A presentation of this nature helps us to keep in mind the irritating phase of this pathological picture, with the struggle between squamous and columnar epithelium, resulting in the abnormal cell proliferation and growth. In a paper by George V. A. Brown before the Section on Gynecology of the Southern Medical Association, attention was called to the results in these cases treated by various methods. The printed text of his paper failed to include the figures given in his presentation. However, the end results of treatment showed a very low incidence of malignancy, much lower than would be expected in a similar group of untreated cases having this type of lesion.

Most significant in this presentation, are the statements, with which I agree, namely: " . . . eversions of the cervix rarely have recurred following treatment, when the delivery subsequent to treatment was normal," and "all cervices can be restored to a hypothetically normal condition if treated early, by the destruction of heteroplastic endocervical tissue."

DR. EMIL NOVAK, Baltimore, Md.—In his paper, Dr. Mohler has more or less restated some old ideas as to the lesions he has discussed, but has expressed other views not in keeping with accepted concepts. He has particularly emphasized the congenital nature of the displacement of the endocervix in cases of cervical erosion, and in this respect I believe he is in error, except in the case of a lesion which he did not discuss, the so-called congenital or Fischel type of erosion. The latter is due to the fact that the line of demarcation between the squamous and cylindrical epithelium, normally at the external os, is sometimes located more distally, so that an areola of endocervix surrounds the os, presenting as a reddish congenital erosion. This is of little or no clinical importance.

It must be remembered that in the early embryonic stages the squamous epithelium extends well upward into the canal, later receding, but leaving behind it certain cells with the potentiality of producing squamous epithelium in later life, and this probably explains at least some cases of so-called squamous metaplasia, though the majority are probably the result of the inflammatory changes found in the common acquired type of erosion. A distinction must be drawn between three lesions of the cervix which are often confused. These

are ectropion or eversion, erosion, and ulcer. The latter implies an actual destruction of the surface integrity, with a granulation tissue base, the best example being the decubitus ulcer on the prolapsed cervix.

An ectropion, like the corresponding lesion of the eyelid, simply means a rolling out or eversion of the affected mucous membrane, usually because it is so swollen and thickened that there isn't room for it within the canal. It rolls out just as does the lining of a sleeve if it is too long for the cloth. Ectropion is often seen in association with lacerations of the cervix, but may at times be seen in the intact cervix.

The cervical lesion of this general group which has excited most interest is the acquired erosion, and, as Dr. Mohler has mentioned, one of the earliest studies of this subject was that of Adair, who was then, I believe, working in the laboratory of Robert Meyer. However, Dr. Mohler made no mention of the subsequent studies of Meyer himself, in spite of the fact that these have been accepted as of fundamental value. For example, they refute the idea that the displacement of the endocervix is congenital, but emphasize the interplay between the two types of epithelium in the active and healing stages of chronic cervicitis. I feel sure that the women in whom Dr. Mohler described a supposedly congenital displacement of the cervix would have shown normal cervices if he had had a chance to examine them in early life, before the trauma of childbirth, and would have shown no suggestion of such a congenital dislocation of the cervix as he assumes.

DR. JAMES E. DAVIS, Dexter, Mich.—Cervical tissue possesses a high degree of tolerance to trauma, infection, and congenital defects. Our esteemed and deceased member of this Association, Dr. J. Henry Carstens, frequently declared it was the most abused part of the body. Detection of its major pathological changes is usually successfully made by competent and careful observers.

Biopsies of cervical tissue to confirm a diagnosis of malignancy involve experienced selection of areas. Recognition of hyperplastic and hypertrophic areas producing irregular boundaries is of great value in pointing to the most likely site of a malignancy.

Prepared microscopic sections should be well made. The pathologist should follow the experience which has yielded him a satisfactory guide to safe diagnoses. First attention should be given to the normality of the stratified epithelium and next of the glandular epithelium. The stroma is examined last, especially in erosions, where all of the stratified epithelial cells may have departed from normal. Metaplastic changes in the presence of infection should be critically studied.

In a personal study of 1,200 cervices, malignancy was found in 186 and in 39 there were benign neoplasias.

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—Study of the cervix, especially at the extremes of life, as in the newborn infant and the senile woman, shows, as Dr. Novak has indicated, that there is marked variation in the location and appearance of the stratified squamous epithelium. There are two stimuli which cause change in the location of the mucocutaneous junction between the endocervical epithelium and the stratified squamous epithelium. One is infection, and the other is apparently endocrine stimulation. In the newborn infant, possibly at puberty, during pregnancy, and during the senile period, especially under endocrine stimulation, the reserve cells which are situated beneath the ectocervical and endocervical epithelium, and which are multipotential, are stimulated not only to form new glands but to grow outward and replace the normally occurring boundary between the two types of epithelium. I would like to state, therefore, that the picture of the cervix is never at any time in a woman's life a static one, but receives stimuli to growth both in its glands and in its epithelium during periods of endocrine stress. It seems to me that one of the most important points in Dr. Mohler's paper and one which might be passed over is that he focused attention on the endocervical epithelium as a source of difficulty especially as it concerns carcinoma.

DR. MOHLER (Closing).—I knew I was going to get into trouble when I made this presentation because Dr. Novak, whose opinion I respect highly, had previously commented

on my views. I have studied almost all of the works on endocervical lesions but I did not refer to them in this presentation since I wanted to emphasize only a few clinical points.

So far as punch biopsies are concerned, I admit they may be inadequate but I do feel that spot biopsies have a good deal of value when they are taken from an abnormal area by a trained observer who recognizes a focus of disease. I believe if we are careful in our examinations we can usually recognize changes in the cervix which may be significant. I think the point expressed by Dr. Paddock is the one which should be followed. We should do a complete biopsy whenever possible but I doubt if it would be practical in all cases since in our own series we found that 53 per cent of nulliparous and virginal women had eversion or erosion of the cervix. It would be prohibitively expensive and probably useless because many of them are young women who have nothing except what I consider misplaced endocervical tissue.

There are two important reasons for this presentation. The one reason is to try to introduce to physicians who are interested in gynecological examinations a standard for the evaluation of the normal cervix. The other reason which I think is very important is the large number of nulliparous and virginal women observed with eversion or erosion of the cervix. These abnormalities I have considered congenital and I believe they meet the standard which Dr. Novak has just expressed. As I have demonstrated in my own experience the everted and eroded cervix can be restored to normal by treatment. The method of treatment is not pertinent to this presentation. The specimen for biopsy can usually be excised with the endotherm. Recently, after collaborating with our pathologists, we have decided to do a series of biopsies, which have been carefully excised with the endotherm for histological study, in order to determine if they are satisfactory. Specimens suspected of malignancy will not be included in this series. The ideal, of course, would be to do serial sections on every cervix which has misplaced endocervical tissue or heteroplastic endocervical tissue present, but this is not practical, and I do not know if we shall be able to do such a study.

Erosions and eversions of the cervix and their origin are a didactic subject and require a great deal more work and a little different perspective than has been demonstrated in existing literature. I hope before I finish working that I might be able to make my convictions more obvious.

THE PRODUCTION OF ACTH IN THE PATIENT UNDERGOING GYNECOLOGIC SURGERY OR RECEIVING PELVIC IRRADIATION*†

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(From the Department of Gynecology and Obstetrics, The Ohio State University College of Medicine)

DURING recent years the concept of the general adaptation syndrome, and the alarm reaction which initiates it, has become a part of our medical thinking. Whether or not one accepts the entire concept as elaborated by Selye, the sequence of events which he postulated as occurring in response to stress has been sufficiently substantiated to serve as a basis for much of the contemporary endocrine investigation. That this sequence of events does not represent the entire story of the pituitary-adrenal axis relationship can be admitted without invalidating it as a contribution.

In its most simplified—or oversimplified—form, this sequence of events proceeds as follows (Fig. 1): Stress applied to the body mechanism results in the production of epinephrine from the adrenal medulla. This acts, probably through the hypothalamus, on the pituitary, with the resultant production of ACTH. The ACTH, in turn, acts on the adrenal cortex to stimulate the production of cortisone (and related steroids). The production of cortisone by the adrenals is associated with (and in some instances is the cause of) certain characteristic changes in the metabolism of sugar, sodium, potassium, nitrogen, as well as in alterations in the lymphocyte count, the eosinophil count, the 17-ketosteroid production, etc., etc.[1, 2]

The changes in the white blood cell elements have proved the most convenient clinical technique for measuring this response on an acute or short-term basis, and the Thorn test simply stimulates this chain of events by the administration of exogenous Adrenalin. On a more long-term basis, the metabolism of the various ions which are influenced by cortisone has proved the most feasible method of demonstrating the bodily production of ACTH.

While there are many factors which influence the metabolism of sodium, potassium, and nitrogen, it is also true that if most of these factors can be controlled (the amount and consistency of the intake of these ions, the fluid intake, the activity of the subject, etc., etc.) then the administration of ACTH will produce a pattern of changes which is entirely characteristic for it (Fig. 2). Fig. 3 records the metabolic balance study on such a healthy subject. On a constant, adequate but not excessive, intake of these elements, the subject soon stabilizes at "balance zero" with the measured output equaling the

*The work reported here was carried out under a research grant issued by The Department of Public Health of the State of Ohio.

†Presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

intake. Under these circumstances the administration of ACTH will result in sharp sodium retention, with spilling of potassium and nitrogen. The daily eosinophil and lymphocyte counts show a tendency to decline, and the 17-ketosteroid excretion rate rises.

Using this pattern of metabolic response as well as other indices of bodily ACTH production, Harrower,[3] Forbes,[4] Kelso,[5] Venning,[6] and Stevenson[7] have reported investigations which indicate that a surgical procedure represents a stressful situation to which the patient responds with a typical alarm reaction. The pituitary is stimulated to increased activity, ACTH (at least) is elaborated, and the metabolic changes previously outlined can be observed during the postoperative period.

The present study was undertaken primarily to determine if there is a corresponding "alarm reaction" which takes place in the patient with pelvic malignancy who is undergoing therapeutic irradiation. No study of this type had previously been carried out, and the impact on the patient's metabolism of therapeutic radiation was unknown. That irradiation of the pelvis might well provide a stressful situation, and that such stress might well result in the production of ACTH by the patient's pituitary seemed logical suppositions. To turn such suppositions into facts or to deny them might conceivably alter our care of the woman under therapy, or even improve our entire radiation management.

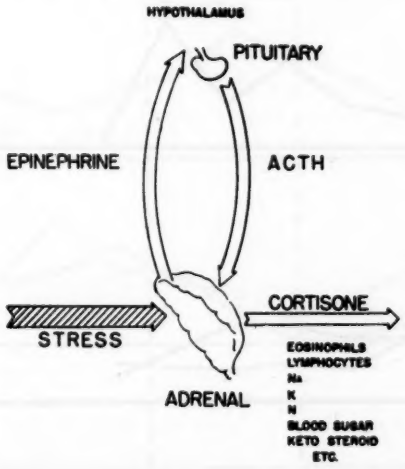

Fig. 1.—Diagrammatic representation of some of the sequence of events in the alarm reaction phase of the general adaptation syndrome.

Since direct measurements of ACTH or cortisone are not at present feasible, the determinations of the patients' production of these hormones has been achieved by simultaneous careful balance studies of sodium, potassium, and nitrogen, together with daily 17-ketosteroid determinations, eosinophil and lymphocyte counts. Since, furthermore, quantitation of the degree of pituitary activity measured in this fashion has been in no way standardized,

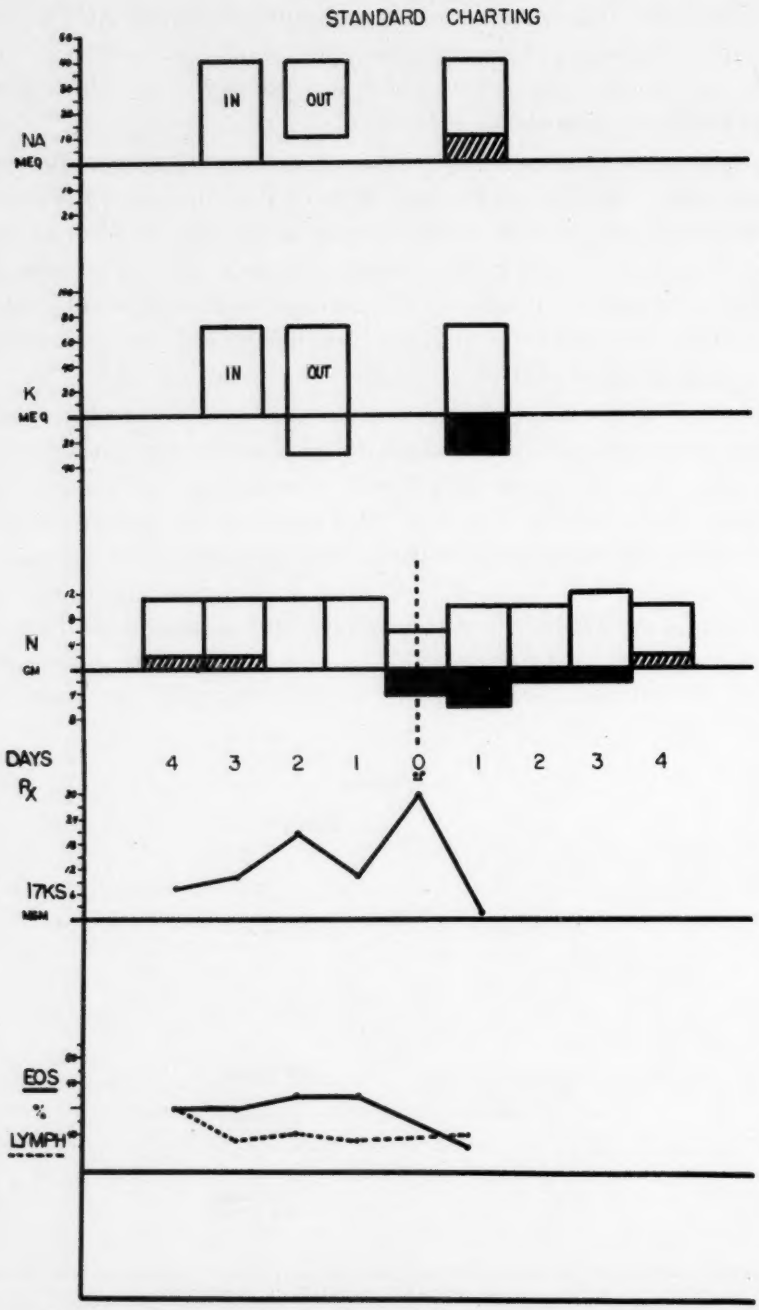

Fig. 2.—Standard charting used in these balance studies. The intake is charted from the base line upward (see top line). The output is charted from the top of the intake line downward. When these two are superimposed for the balance of that particular day, the difference is represented in a shaded area above the base line if the output was less than the intake (right-hand figure on top line). If the output exceeds the intake, the difference is represented by a solid black area below the base line (right-hand figure on second line). The sequence of days on the third line represents two days of retention, followed by two days in "balance zero," followed by four days of an output which exceeds the intake, etc.

Sodium (top line), and potassium (second line) are charted in milliequivalents. Nitrogen is charted in grams. 17-ketosteroids and the eosinophils (solid line) and lymphocytes (broken line) are charted below.

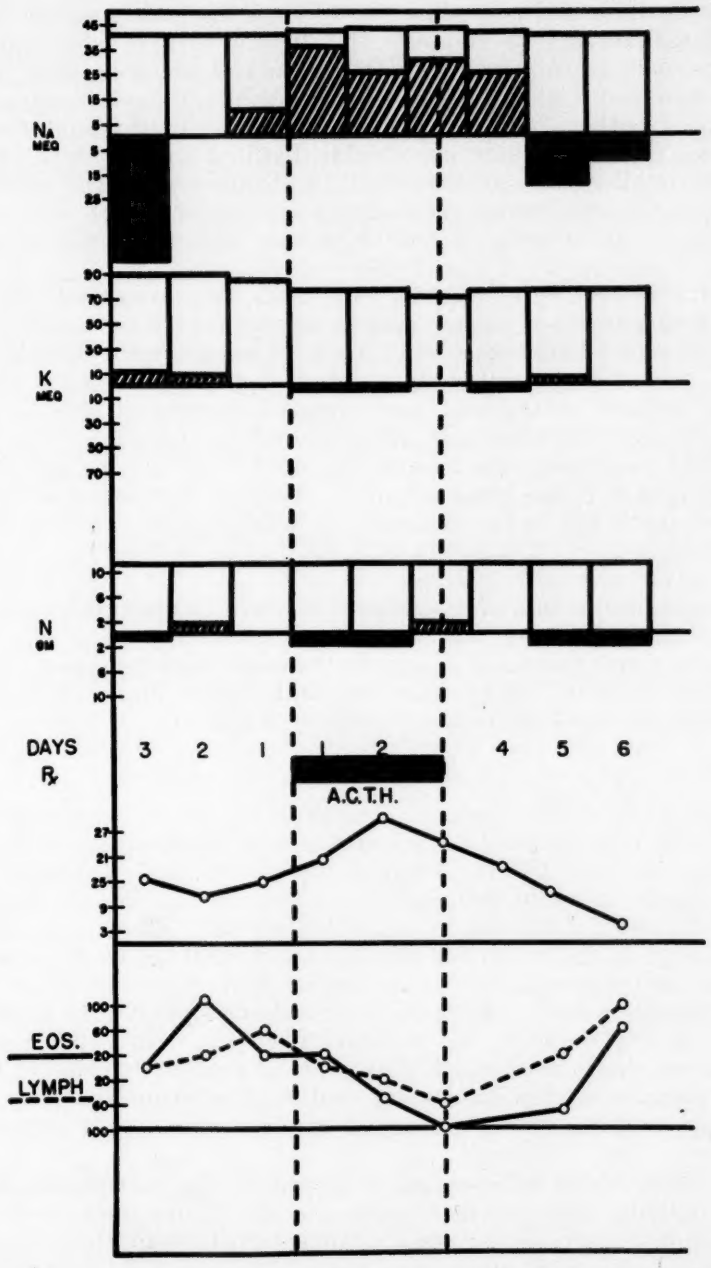

Fig. 3.—Reaction of a normal patient following ACTH. (See Fig. 2 for chart reading.) A normal patient initially on three days of the standard diet, followed by two and one-half days on ACTH. There is a sharp retention of sodium with a tendency to spill potassium and nitrogen. The 17-ketosteroids rise initially, later to fall to a depressed level. The eosinophils and lymphocytes are depressed.

the amount of change observed has been compared with that seen in a group of patients who have undergone familiar gynecologic operative procedures.

Methods of Study

A Metabolic Ward was instituted for the purpose of these particular balance studies. After a few analyses of the dietary components by flame

photometer (sodium and potassium) and by the Kjeldahl method (nitrogen), it was found satisfactory to compute the dietary intake, weighing component parts of the diet carefully and calculating the sodium, potassium, and nitrogen from the standard (Mead) chart. The individual food items on each tray were weighed both in and out of the room, and the amount consumed calculated. All drinking water was double-distilled water. A full-time trained dietitian made all intake measurements, and interviewed the patients at least twice a day to ensure against their eating food from outside sources, or (more frequently) saving an item of food from one 24 hour period to eat it in the next.

All urine was collected on a 24 hour basis, measured, and aliquot samples taken for determinations of sodium and potassium (flame photometer), nitrogen (micro- and macro-Kjeldahl) and 17-ketosteroids (Drekter and coworkers[8]). Feces were collected, weighed, homogenized with triple-distilled water, and sodium, potassium, and nitrogen determinations carried out on aliquot portions. Carmine was administered by mouth on the day of admittance, and its appearance time in the stool dated the relationship between the stool output and the intake figures. Vaginal bleeding and wound drainage, where significant, were obtained by washing out dressings or linens in triple-distilled water. The study was conducted during the winter months, and perspiration was not measured.

The eosinophil counts and lymphocyte counts were obtained at a constant hour each day; because of the relatively constant nature of the meals, however, it was not felt indicated to obtain them in a fasting state. The patients' weights were recorded every morning, and within limits the patients were maintained on the same approximate degree of activity.

Subjects

Careful (and tedious) balance studies of the above type were carried out in 12 patients, in addition to the controls who received no therapy and the controls who received ACTH. Of these twelve, six were subjected to various surgical procedures while their metabolic balance was followed; six received intrapelvic irradiation for carcinoma of the cervix. All of these patients were first maintained on the relatively standard diet until the intake and the output of the elements being measured were approximately equivalent and they were close to "balance zero." All were followed postoperatively until they were back to, or nearly back to, the preoperative state. No balance study lasted less than seven days, most considerably more, and in the case of some of the irradiated patients studies have been continued intermittently up to 104 days post therapy, seeking possible delayed manifestations of increased pituitary activity.

For reasons which will become apparent as the results are discussed, six additional patients with cervical carcinoma had Thorn tests carried out in an effort to evaluate the responsiveness of their pituitary-adrenal cortex axis.

Results

The results of such a study for any individual patient are best indicated by the graphic form shown in the figures which illustrate this paper (see Fig. 2 for chart reading). It is neither desirable nor feasible, however, to reproduce in detail the outcome of each of these studies on every subject. Characteristic studies of individual patients are illustrated, and the response of the groups is discussed. In general, sodium proved the most labile element, with wide swings of both retention and spillage. The depressions in the white cell elements were mild in comparison with those seen after the injection of

Adrenalin. *With all other metabolic influences controlled, the pattern of sodium retention with the spilling of potassium and nitrogen, together with a passing depression of the white cells studied and a brief increase followed by a drop in 17-ketosteroid level, was interpreted as the characteristic pattern indicating the*

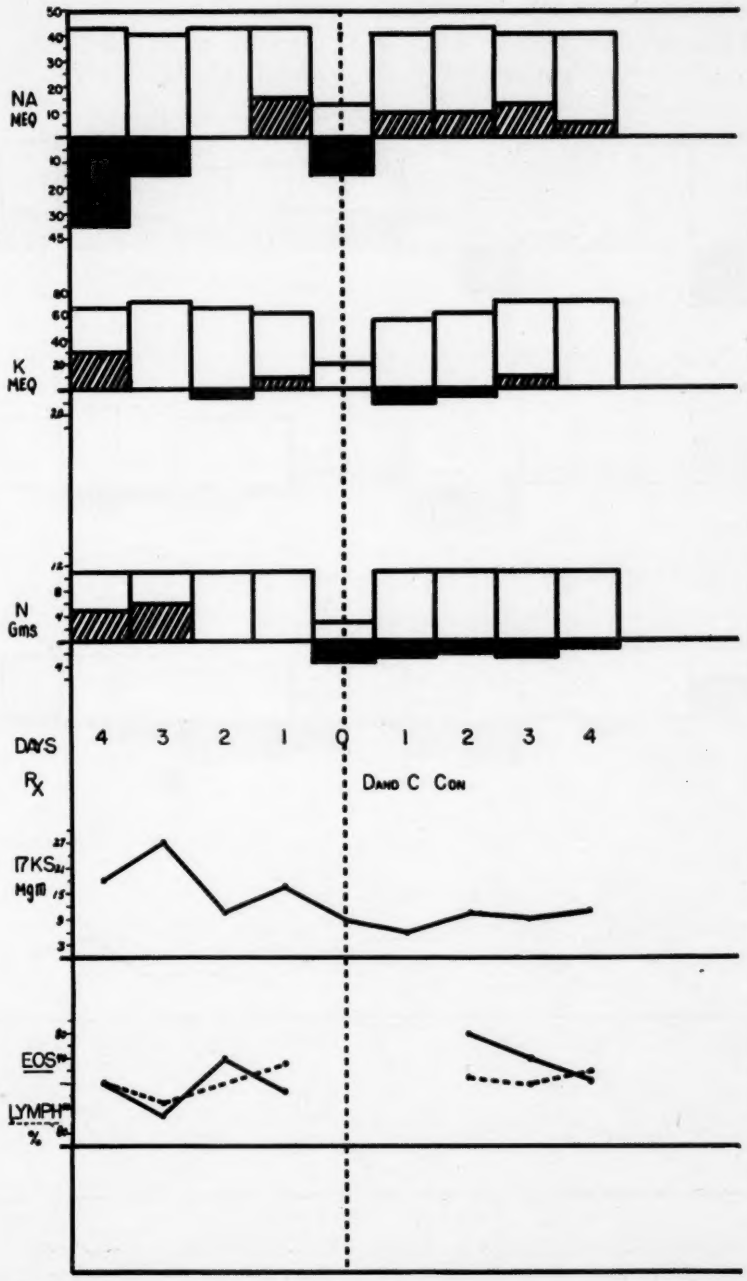

Fig. 4.—Reaction in a patient following minor gynecologic surgery. For the few days following the performance of a curettage and cervical conization, the patient displays sodium retention with some tendency to spill potassium and a negative nitrogen balance. The brief passing peak of 17-ketosteroid excretion (often occurring only the day of surgery) was not caught, but the postoperative depression is well shown. For technical reasons the white cell counts could not be obtained the day of surgery and the first postoperative day.

elaboration of ACTH by the patient's pituitary. These changes, under such circumstances, have been sufficiently observed by others, and could be easily enough reproduced in our hands by the administration of ACTH (Fig. 3) to justify such an assumption.[2, 9, 10]

The Patients Operated Upon

Fig. 4 records the balance study on a patient on whom a dilatation and curettage and cervical conization were performed. After a four-day period

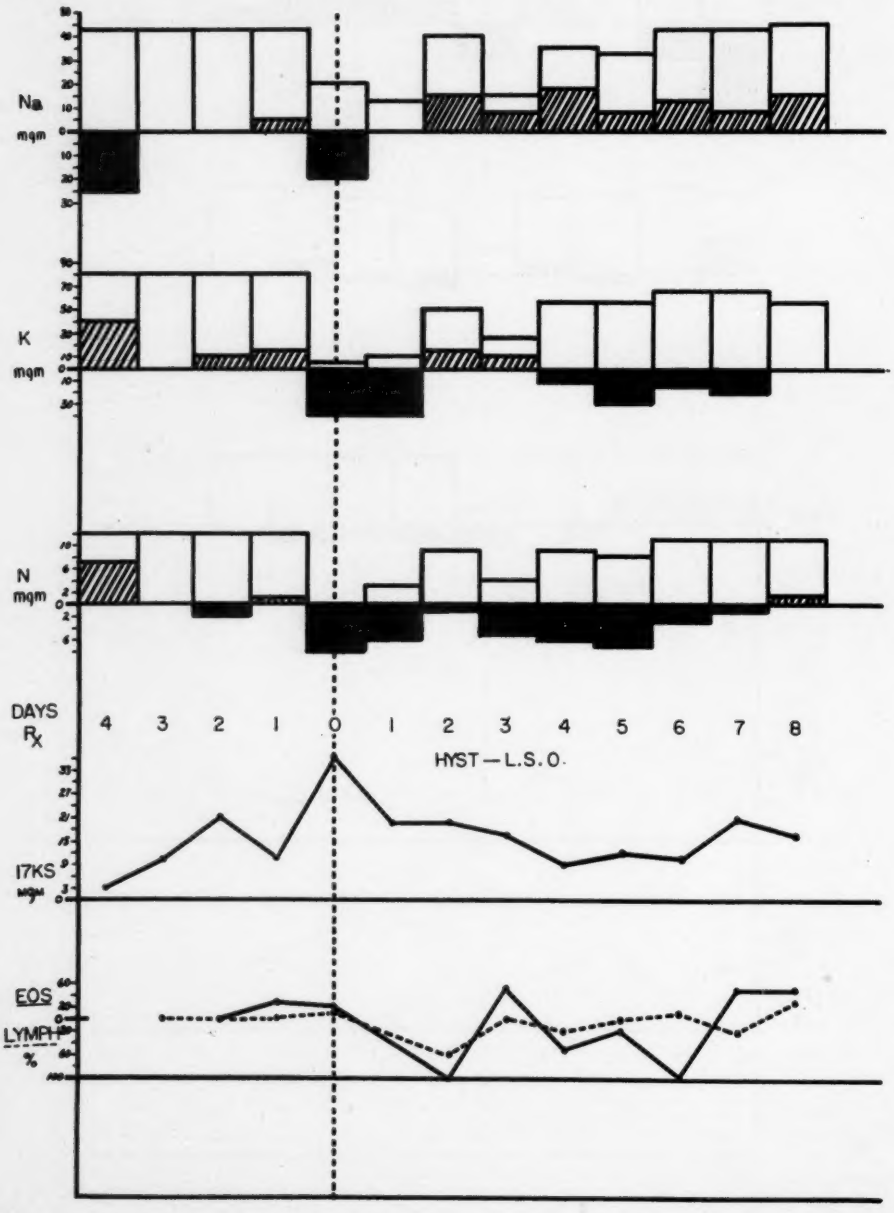

Fig. 5.—Reaction in a patient following major gynecologic surgery. The balance studies following a total hysterectomy with preservation of one ovary. The patient presents a very typical picture of the alarm reaction persisting for seven days in the postoperative period.

to establish metabolic equilibrium, the performance of the operative procedure provided the stress which resulted in the elaboration of ACTH during the next few days. For the postoperative days the balance pattern reduplicates (with a minimal 17-ketosteroid reaction) that seen in Fig. 3 during the administration of ACTH. This period of positive sodium balance, negative potassium and nitrogen balance is brief, and the depression in the eosinophils and lymphocytes is mild and the 17-ketosteroids show only their postoperative fall.[11] The surgical insult has been minor, and the alarm reaction which results is definite and unmistakable, but not extensive.

By way of contrast, the patient whose reaction is recorded in Fig. 5 was subjected, after an initial period of observation, to a major surgical procedure (curettage, laparotomy with total hysterectomy, bilateral salpingectomy, and unilateral oophorectomy*). It can be seen that the patient's balance studies reveal the same pattern, but that the pituitary's elaboration of ACTH persists for a longer period of time. Whereas the alarm reaction of the patient who had the curettage and conization was limited to a few days, the patient shown in Fig. 5 displays the identical reaction, but continuing for a greater period of time. The changes are the same, and indicative of the same fundamental bodily response; the duration of this response is greater for the more extensive surgical procedure.

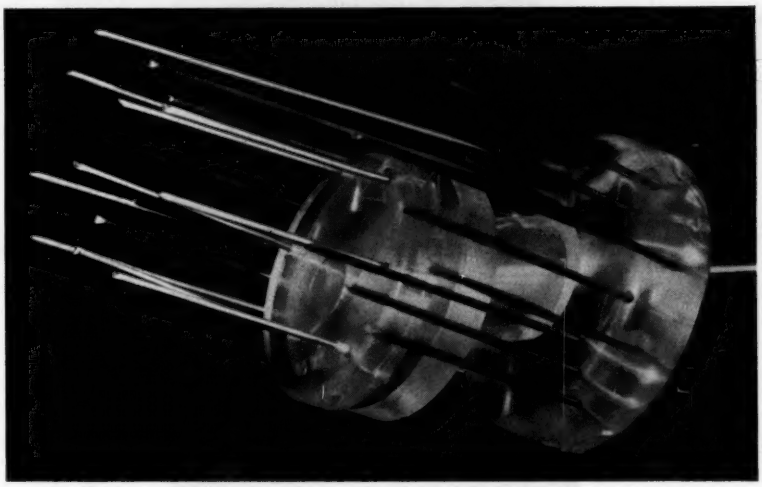

Fig. 6.—Vaginal plastic templates with needles of the type used to irradiate the pelvis in this study.

With all of the patients in this group, this phenomenon was observed. After a period of metabolic balance, the surgical procedure would result in a pattern of bodily response which was identical with that seen on the administration of ACTH. In general the duration of this response was proportionate to the extensiveness of the surgery; not the degree of deviation from balance zero, but the duration of the response, was the criterion of surgical extensiveness.

Comment.—These findings confirm for gynecologic operative procedures what has been observed in other forms of surgery,[12] namely, that an operation

*Because of the known effect on the pituitary of castration, the patients in the group operated upon were so selected that none required bilateral oophorectomy. Our interest here is in the impact of the operation on the pituitary-adrenal axis, rather than the impact of castration. Likewise, in the irradiated group, since the external x-ray therapy had preceded the measurements of the impact of the intrapelvic radiation, all were postmenopausal, and the procedure being studied did not, in itself, cause castration.

represents a form of stress which results in the elaboration of ACTH by the patient's pituitary. In this instance such pituitary activity has been followed by its metabolic impact on the patient's sodium, potassium, and nitrogen, by its effect on the lymphocytes and eosinophils, and by the excretion of the 17-ketosteroids.

These findings serve to emphasize the disadvantage of considering the postoperative response of a surgical patient as a series of isolated metabolic phenomena. Considerations of the sodium metabolism or of the potassium balance which fail to recognize that these are related indices of a generalized body response are incomplete considerations. Actually, it has not been clearly demonstrated that for a patient to undergo the alarm reaction postoperatively is necessarily detrimental to that patient, and speaking of "correcting" the potassium "imbalance" in a postoperative patient is to reason from assumptions open to question in the light of the findings here reported.

Fig. 7.—Anteroposterior and lateral x-rays of a patient with this type of irradiation unit in place (only the tiny sources of cobalt^{60} show on the x-ray).

The Irradiated Patients

The group of patients whose pituitary response to radiation was studied had cervical carcinoma ranging from League of Nations Group II to League of Nations Group IV. All had received external x-ray therapy which had delivered between 2,000 and 2,200 r to the tumor. As with the group operated upon, all were admitted and observed until the metabolic balance had reached equilibrium prior to the institution of intrapelvic therapy.

These patients were all irradiated with radioactive cobalt, using the technique previously described by us[13, 14] (Figs. 6 and 7). By this method an even

blanket of irradiation can be administered to the entire pelvic cavity without a "hot spot" of concentrated treatment centrally and a diminished dose at the pelvic walls. The therapy was so adjusted that the entire pelvis would receive 1,000 gamma roentgens per day.

Since this technique requires the use of vaginal templates and interstitial needles, it became necessary to determine how much pituitary stimulation resulted from the implantation of the needles and needle holders, without any

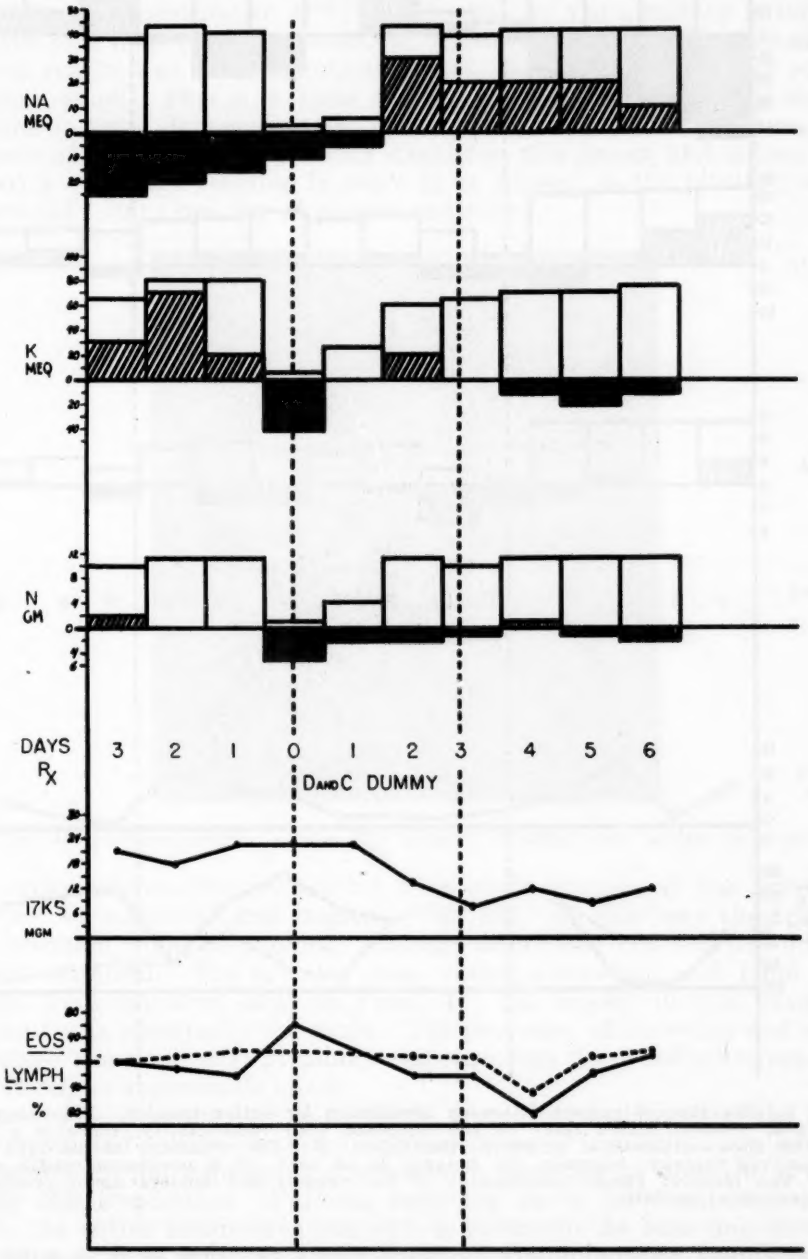

Fig. 8.—Reaction of patient following insertion and removal of inactive needles. The insertion, and particularly the removal, of the vaginal templates and needles (nonradioactive in this patient) creates pituitary stimulation with the characteristic metabolic changes.

radioactivity. For this purpose a patient was selected, and the vaginal form with hollow, non-cobalt bearing needles was inserted under general anesthesia. The studies on this patient are indicated in Fig. 8. It can be seen from an inspection of this chart that the implantation or the removal (under anesthesia)

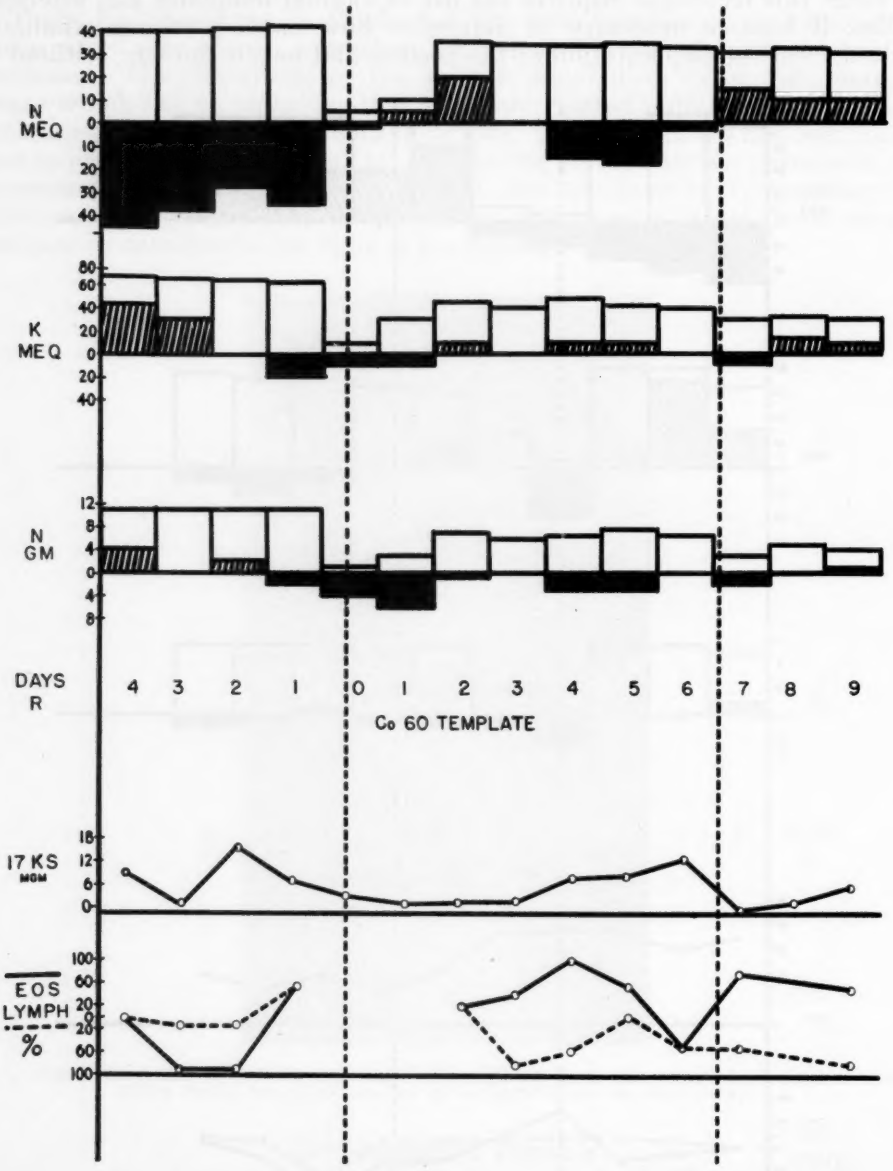

Fig. 9.—Reaction of patient following irradiation by active needles. Following the insertion (first vertical dotted line) of the template with radioactivity, there is a two-day period which shows evidence of pituitary stimulation. For the remainder of the days that the patient receives therapy, however, the balance is at zero, or a noncharacteristic group of changes. The removal (under anesthesia) of the needles and holders again precipitates a minimal (one day) pattern.

per se produced approximately as much alarm reaction as does a curettage with conization (Fig. 4). Both the insertion and the removal of the interstitial needles had an effect on the patient reflected in her metabolic balance, but

both were short in duration. From this it could be concluded that any increase over this rather minimal amount of pituitary stimulation would be attributable to the irradiation itself.

Fig. 9 reproduces the course of a patient implanted with the same type of applicator, but with the needles loaded with radioactive cobalt which would provide the daily dose of 1,000 r. It can be seen that in the first few days after implantation the patient presents the characteristic pattern of sodium retention with potassium and nitrogen loss. Again after removal of the needles this same picture of ACTH production by the pituitary is indicated. But in the four days preceding removal, when the patient had recovered from the alarm reaction of the implantation itself, there is *no evidence of pituitary stimulation at all. This is in spite of the fact that a rather heavy dosage of irradiation is being delivered to the entire pelvis each day.* This same finding was observed in each of the patients studied in this group, and it became evident that a curettage resulted in more of an impact on the pituitary-adrenal axis than did 1,000 r per day of gamma radiation.

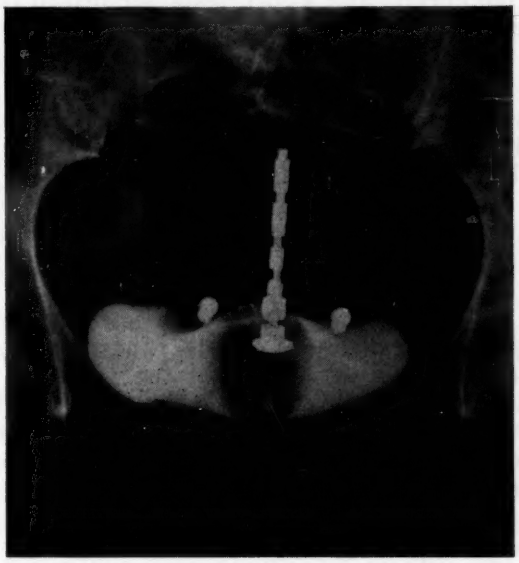

Fig. 10.—Anteroposterior x-rays with cobalt^{60} colpostat and tandem in place.

In order to consider this finding from another angle, it was arranged to apply Co^{60} by colpostat and tandem (Fig. 10). In this way the trauma of needle insertion could be avoided, although anesthesia and cervical dilatation were still required. The per day dose varied somewhat, and 1,750 gamma roentgens were delivered daily to Point *A*. The impact of this program on the patient was essentially the same. The processes of insertion and removal each caused some minimal pituitary response, but the irradiation apparently had, of itself, no appreciable effect.

Comment.—It seems safe to conclude, from the consistency of the findings in the irradiated group, that therapeutic doses of radiation applied to the pelvic cavity do not represent as stressful a situation as does the process of inserting this irradiation. Patients receiving up to 1,000 gamma roentgens a day to the entire tumor area can and do return to the base line where they are at balance zero with an average eosinophil and lymphocyte count and a normal 17-ketosteroid level. The pituitary, in other words, does not respond even to the extent it would to minor surgery.

In the light of these observations, two questions require answers. The first is: Is the effect of irradiation a delayed effect which will become manifest at a later date? Is the patient's alarm reaction, like some other effects of bodily irradiation, only apparent many weeks after treatment? In an effort to answer this question, three patients were recalled at monthly intervals to remain in the Metabolic Ward from four to seven days for further evaluation. These secondary studies were continued up to 104 days post cobalt in one case, in the search for evidences of a delayed alarm reaction. Aside from two occasions when the patients were suffering from a rather severe bowel reaction, there was no indication of pituitary-adrenal activity.

The second question is perhaps more subtle: Is this failure to discover evidence of an adrenal-cortex response inherent in the disease rather than in the therapy? In other words, since the study group had in common not only the radiation which was being investigated, but also carcinoma of the cervix, was the lack of an alarm response due to the latter rather than the former? To answer this question another group of patients was selected, all with carcinoma of the uterine cervix, and Thorn tests performed to check the responsiveness of the pituitary-adrenal axis.

The Thorn Tests

Six patients with cervical carcinoma had morning eosinophil counts performed immediately after eating a fairly standard diet. Two-tenths of 1 c.c. of 1:1,000 Adrenalin was then administered subcutaneously, and the eosinophil count followed at two-hour intervals for the next four hours. A depression in eosinophil count which amounted to 50 per cent of the initial count was interpreted as evidence of response in both the pituitary and the adrenal cortex.

All six of the patients studied had initial low eosinophil counts, but all showed sharp drops in the eosinophil counts, ranging from 60 to 90 per cent, and indicating in all instances an ability of the pituitary to respond to epinephrine and of the adrenal cortex to respond to ACTH. In other words, the failure of significant response in the irradiated patients must be interpreted as a failure of roentgen therapy to stimulate the pituitary, rather than a failure of the carcinoma patient to respond.

Comment.—In considering these results, several items must be remembered. In the first place, in the early delineation of this theory, one of the stresses which was applied was irradiation.[15] This produced an alarm reaction, but the amount of irradiation used, in proportion to the size of the experimental animal and the volume of each animal which was exposed, was tremendous. In the present studies we have been concerned with the human patient who is subjected to irradiation in the therapeutic range, and, under such circumstances, the administration of gamma roentgens to the pelvis is relatively without impact on the pituitary.

In the second place, it is interesting to note that earlier hematologic studies had revealed no consistent change in the eosinophil counts under x-ray or radium treatments. Dunlap,[16] in his survey of the bodily impact of irradiation, records the drop in leukocytes resulting from exposure, but indicates that the eosinophil count is random in its behavior and shows no consistent response. In the face of a pituitary impact, the eosinophils would have fallen, so that, although there was no understanding of the mechanisms involved, the earlier findings serve as a preconfirmation for the present report.

Comment

The ultimate significance of these observations must await the answer to the (relatively metaphysical) question as to whether the alarm reaction un-

der these circumstances is beneficial or harmful to the patient. However, the immediate application of these results to our proper evaluation of the metabolic balance of the patient who has been operated upon or of the endocrine impact of therapeutic irradiation is quite evident. Jeffcoate[17] has recently suggested, reasoning from the earlier animal work of Selye, that the therapeutic effect reported from low dosage irradiation of the human ovaries represents an alarm reaction. For such a suggestion to be offered is almost inevitable, but, when considerably larger doses of roentgens fail to produce, in the human subject, evidences of such a reaction, it is unreasonable to expect it from such small doses.

Whether or not the patient undergoing radiation would benefit from the concomitant administration of ACTH—i.e., from the artificial creation of an alarm reaction similar to that seen after surgery—is problematical. Certainly, if a part of our objective in administering such irradiation is to seal off the neoplasm with fibrous barriers, then the lack of production of ACTH by the body is fortunate indeed.

Finally, it behooves us all to remember that, either in our patients undergoing gynecologic surgery, or in our patients with pelvic malignancy receiving therapeutic radiation, the behaviors of the various elements considered here are not isolated changes occurring in a vacuum, but are integrated responses of a unified complex organism.

Conclusions

The alarm reaction is that aspect of the general adaptation syndrome during which the pituitary increases its production of ACTH with a resultant elaboration of cortisone by the patient.

The present study has measured this reaction in (a) patients undergoing gynecologic surgery, and (b) women with cervical carcinoma receiving pelvic irradiation. These observations have been carried out by determining the impact of cortisone on the metabolic balance of sodium, potassium, and nitrogen, by following the eosinophil and lymphocyte counts, and by measuring the 17-ketosteroid production.

A pituitary-stimulating effect of surgical procedures has been demonstrated, the duration of the reaction observed being roughly proportionate to the extensiveness of the surgery.

Pelvic irradiation is marked by a singular lack of an alarm reaction, with little or no evidence that in therapeutic ranges radiation provides a stressful stimulus.

The significance of these various findings is briefly commented on, and questions for further study are raised.

The author wishes to express his appreciation to Dr. Irving Rothchild and to Dr. Leo Sapirstein for the determinations carried out in their respective laboratories.

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THE NEWER GYNECOLOGY: SOME OF ITS SURGICAL AND ANATOMICAL IMPLICATIONS*

C. McINTOSH MARSHALL, F.R.C.S. (ENG.), LIVERPOOL, ENGLAND

BY YOUR generous invitation, given with scarcely a thought of my incapacity for the task, you have laid upon me the pleasant duty and very high privilege of delivering the Joseph Price Oration. This is then, first and foremost, a day for remembrance. Let us recall for one moment the man to whose memory this occasion is reverently devoted. When I look back upon his career, upon his teaching, upon the inspiration which for so many years he breathed into the thought and practice of his day, I think of him not only as one of the greatest of your surgeons but also as the priceless possession of the wider world of surgery and surgical endeavor.

It has been said that he was bitter and unrelenting as a foe, that he showed an aggressive militancy, a strong bias, impulsive likes and dislikes, and even a degree of jealousy of his near-by and successful competitors. What of it? They were weaknesses of a very common order and infirmities which did not in any way disfigure his career. In these very human frailties also lay his strength; they show that Price was a man of strong feelings and deep conviction and indeed without these traits it is difficult to imagine how he could ever have contributed something of genius, and so much that was permanent and vital to the progress of surgical art. There was small place for humility and sweet reasonableness. Whenever Joseph Price had a message he based it first on irrefutable evidence, developed it with inexorable logic, then spread it abroad with the faith, heat, and fire of a true evangel. Listerism and asepsis were in the air, the new pathology was appearing, and he was one of the first to sense that a surgical revolution was in progress. Price grasped his opportunities. He made original and outstanding contributions particularly in the field of pelvic inflammation, extrauterine pregnancy, and fibroid tumors. Eloquent and inspiring as a teacher, skillful and graphic in debate, he quickly came to be acknowledged as the outstanding mouthpiece for much that was to prove durable and unassailable in the newer surgery of his day.

But however great his eminence in all these matters, his excellence in the field of operative surgery, abdominal and pelvic, was surely unequaled in this country during the two decades which hinged on the turn of the century. This was clearly his greatest enthusiasm, the one into which he threw his whole body and soul, and the one which was to gain him a distinction and renown not confined to the borders of this great continent. "He taught constantly by and

*The Joseph Price Oration, presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

through his operations." It was the recollection of these words, written by Kennedy in 1912, which drew me to the choice of a subject for today's Oration.

This choice has caused me some concern for I must confess I have been astonished at the scope, the variety, and the distinction of the Orations presented here by my illustrious predecessors. In making it, then, I hope you will not think I have approached this invitation lightheartedly or taken an unfair advantage of the generous terms in which it was couched.

"The subject of my own choosing" embraces, then, some little bits of many things. It briefly describes some operative procedures; it tries to illustrate the assistance that art and pictorial aids can render to our teaching; in the main, however, it attempts to stress the importance of structure in all our surgical work. For speech might be likened to operative technique and eloquence to an intimate knowledge of living anatomy. With the former alone any of us can get by, but it is only the latter that can give smoothness, rhythm, and easy fluency to both our thought and our actions.

"Slings" and Stress Incontinence

In any remarks on the newer gynecology the subject of stress incontinence cannot be entirely overlooked. Slings passed wholly by use of the abdominal route must inevitably surround the vesical neck rather than the true urethra. Most of those placed by a combined exposure lead to the same result even when attempts are made to secure the fascia to the urethral floor by suturing. All this would seem logical in view of the radiological discoveries of the behavior of the vesical neck in cases showing stress incontinence. Yet a sling which exerts its chief effect at this site can in an appreciable number of instances substitute for the incontinence a degree of difficult or disordered micturition which may be a disappointment to the patient and an embarrassment to the surgeon. My own results have been distinctly bettered by an operation which aims to support in the most simple way that part of the urethra which lies well below the true urethrovesical junction. Fascia lata was used until recently, when we have come to experiment with the use of ox fascia, thus greatly reducing the amount of operative work. As the urethra is firmly united to the vaginal wall, sharp dissection is required to separate it over a distance of 2 cm. The opening made into the urethrovaginal septum is just sufficient to allow the tip of the index finger to be passed outward and upward lateral to the urethra and to break down by pressure some of its lateral supports. Care is taken not to separate the urethral and vaginal wall as high as the bladder, for it is only by leaving them in anatomical contact that the fascia when tightened can be prevented from ascending to the vesical neck. A small transverse incision is now made along the upper border of the symphysis and this is deepened until the rectus fascia is reached. This and the underlying rectus tendon are pierced to the right of the midline by a slender and suitably curved forceps. The tip of the latter is passed downward in light contact with the bone until it meets the tip of the vaginal finger, which guides it into and through the small vaginal incision. The points of the forceps can, if misdirected, wander forward through the obturator foramen. When passed correctly they just miss the medial border of

the pubococcygeus muscle and the only resistance is that offered by the structures of the triangular ligament. The thread attached to the end of the fascia is grasped and pulled upward into the suprapubic wound. The procedure is repeated to the left of the midline. A half knot is tied in the fascia in front of the lower end of the rectus sheath. This half knot is doubly ligated and the sling is completed. The suprapubic incision is closed with clips and the small vaginal one with a few catgut sutures. The sling remains a true urethral one; it cannot slip up to the vesical neck for the vaginal wall has purposely been left attached to the urethral floor at the upper end of the small vaginal incision. I believe this or some similar urethral sling will, because of its simplicity and effectiveness, still merit some consideration in the management of stress incontinence.

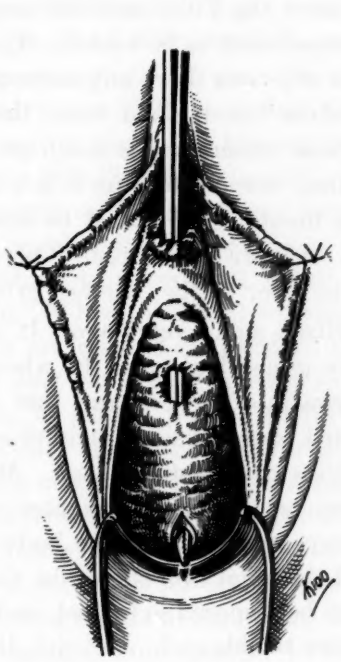


Fig. 1.

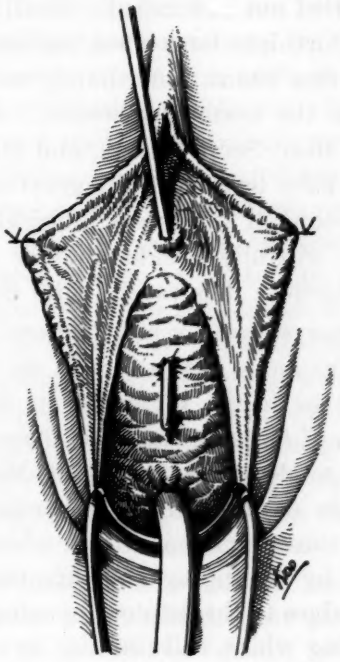


Fig. 2.

Fig. 1.—Colpocystotomy. Incision made onto point of forceps passed deeply into bladder.
Fig. 2.—Foley catheter has been drawn back into bladder. Urethral fistula is now closed.

I have no violent devotion to slings. At the same time I see no reason for throwing them aside just because other operations are appearing on the scene. I can see little difference in the anatomical end results between a sling and a vesicourethral suspension operation of the type so thoughtfully devised and ably carried out by Victor Marshall and Andrew Marchetti. There is, however, one: with a sling there is an additional risk of introducing an obstruction. But this can be avoided by placing it not around the vesical neck but by making it truly urethral.

Colpocystotomy

If a curved forceps is passed deeply into the bladder, its points directed backward, and the bladder and the anterior vaginal walls firmly depressed exactly in the midline, then the vaginal and bladder walls may be safely incised onto these points without any danger to the ureters or their vesical orifices (Fig. 1). A Foley catheter can be drawn back into the bladder, and very efficient bladder drainage is then established (Fig. 2). This should be the first step in the operative cure of most urethrovaginal and vesical neck fistulas for the use of an indwelling urethral catheter after the suture of such fistulas is often fatal to success. I have had the opportunity of using this method of drainage on only four occasions, once in a vesical neck, and thrice in true urethral fistulas. In the latter cases previous repairs with transurethral drainage had been carried out and failed. In all three cases the Foley catheter was removed about a fortnight later when the fistulas were found to be healed. The patients voided urine almost immediately and in no case was there any subsequent leakage from the cystotomy wound. I introduce the method here, first because Chassar Moir, Scott Russell, and others whose experience is much greater than my own have testified to its great usefulness; second because it is a procedure which would at first seem illogical and a mental effort must be made before one can willfully create another fistula to cure one already present; and finally, because it is rarely quite correct to refer to the "newer gynecology."

Colpocystotomy was introduced by Fritsch many years ago. It is interesting too for me to notice that in my country gynecologists on the whole have remained true to the vaginal route in the repair of fistulas and that under the guidance of Chassar Moir they have reverted to the basic principles and simple methods so clearly laid down by Marion Sims and Gustav Simon. Many years ago Simon declared that the operator must recreate with the most meticulous care all those same conditions which in any other part of the body would be followed by healing by first intention; and the chief aim should be the creation of such edges to the fistulous opening as will be disposed so to heal, and a method of suturing which will likewise be conducive to this end. In brief, the method consists in "saucering" or "cratering" the edges and in their apposition by simple interrupted sutures placed so as to leave no dead spaces in the area of union.

Again the operative cure of stress incontinence and particularly its management by "sling" offer together with the above procedure outstanding examples of the weight we should give to surgical history in all our present endeavors. Most of the diagnostic procedures, radiological investigations, cystourethrography, and the prototypes of many of the operations now in vogue can be found in the writings of more than twenty years ago. This is likely true of other conditions and their surgical treatment, and a careful search among things past would, I feel sure, reveal here and there some imaginative idea or practical conception which could only under the safety of modern surgery be brought to full fruition. Thus, others in a different direction might repeat those great

services which Aldridge in your country, and Millin, Read, and most recently of all Jeffcoate have rendered in my country.

Pelvic Lymphadenectomy

A. The Ureter.—

In recent years many earnest, excellent, ingenious and successful attempts have been made to demonstrate in gross and in detail the blood supply of this fascinating structure. The antomical facts are easily appreciated and are widely known. I propose here merely to examine the extent to which the results of these researches can be usefully applied by those of us who are still interested in radical hysterectomy and lymphadenectomy for carcinoma of the cervix. The facts of known usefulness, though few, are of great importance:

1. In at least 50 per cent of cases the pelvic ureter receives a branch from the hypogastric (internal iliac) artery and this when present can be identified by the surgeon and deliberately preserved without any sacrifice to the thoroughness of the operation. If, after the usual classical exposure is made of the brim and lateral pelvic wall, some fine forceps are attached to the cut edge of the posterior leaf of the broad ligament and it and the uterus strongly retracted to the opposite side the ureter usually remains adherent to the peritoneum, follows the movements of the latter, and leaves the pelvic wall. This attachment of the ureter to peritoneum is chiefly due to the fact that some of the vessels which course within its adventitial sheath also give minute twigs to the overlying peritoneum. When the ureter is being detached from the peritoneum tiny bleeding points are created on its deep surface as a result of dividing these twigs. After the duct has been displayed in the foregoing way the hypogastric branch, some 4 cm. in length, will be found coursing transversely inward to reach the ureteric sheath and dividing into ascending and descending branches. Occasionally the accompanying vein is engorged, presents a corkscrew arrangement, and its bifurcating branches can be followed with the eye for their full extent along the fascial ureteric sheath.

2. The pelvic ureter possesses a fascial sheath and in this the longitudinal subdivisions of the main supplying vessels run. It is these that are particularly liable to damage and careless picking at the adventitial sheath with sharp-pointed forceps can tear or rupture them. A spreading red-colored staining of the sheath is then seen to appear.

3. According to some investigators the most constant vessel supplying the pelvic ureter is a branch from the uterine artery. Though it is not suggested that the preservation of this should be part of the operation, the surgeon can occasionally by deliberate dissection demonstrate this branch quite clearly. Out of five such attempts I have succeeded three times. In two instances the vessel arose just lateral to the point at which the uterine artery crossed the ureter. The practical significance of these facts hardly needs stressing. The ureteric branch of the internal iliac, if seen to be present, should be carefully preserved. If the uterine branch is to be saved the uterine artery must be severed medial to where it crosses the ureter. Many will feel, however, that in doing so some sacrifice will be made to the thoroughness of the operation. Finally, and perhaps most im-

portant of all, we are thrown back upon one thing—the preservation of the ureteric sheath and its protection against all rough handling or possible damage. This sheath should be regarded as part and parcel of the ureter and the true muscular wall of the duct should never be exposed. During dissection of the ureter a special type of dissecting forceps, which surrounds but does not crush, is a great advantage. It can contribute much to the speed and effectiveness of the dissection. It can be of particular assistance when picking up the ureter in that final short portion of its course where (with the uterus and vagina placed on the stretch) it sweeps around the lateral and anterior aspects of the vaginal vault, applied to the latter almost like a strap, to enter the vesical angle.

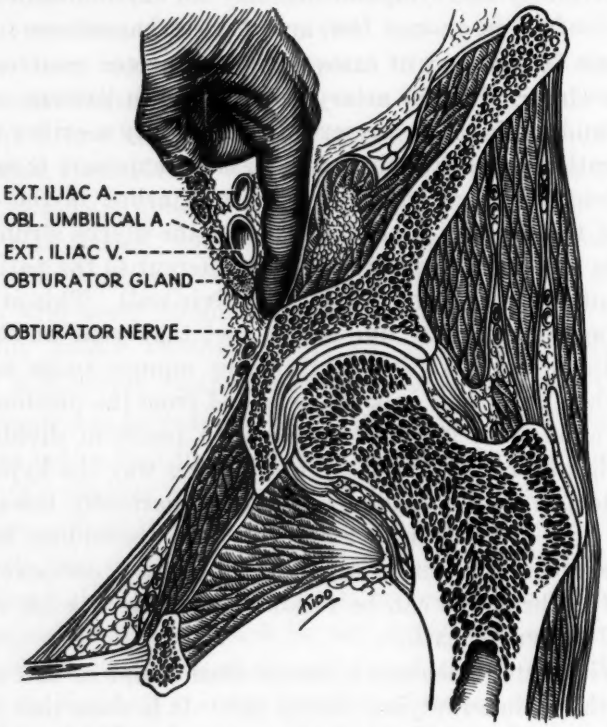


Fig. 3.—Fingers inserted between iliac vessels and pelvic wall and displacement medially of the labeled structures.

B. Glandular Clearance of the Brim and Pelvic Wall.—

There are certain anatomical facts on which I suggest this procedure should be based:

1. The fascial sheath of the external iliac vessels blends external to the artery with the fascial coverings of the psoas muscle.

2. The external iliac vein lies behind, rather than internal to, the artery.

3. When the patient is in a Trendelenburg position the vein is practically empty, a flaccid, loose-walled structure whose edges may not at first be readily visible.

4. The distal limit of the dissection is the point at which the deep circumflex iliac vein crosses the external iliac artery to reach the external iliac vein.

5. Between that point and the origin of the external iliac artery neither artery nor vein gives or receives any branches. The one exception to this may be branches proceeding over the pelvic brim to anastomose with the obturator vessels just as they enter the obturator canal. Occasionally they may constitute the only obturator vessels.

Now it must be conceded that in removing potentially malignant tissue the attack should not proceed through it, but that some plane beyond it should be entered first and the whole mass then displaced medially toward the center of the operative field. I believe the quickest and best way of doing this is first to incise the fascial coverings of the vessels lateral to the artery (and the external group of iliac glands) and along its whole length. This fascia together with that septum projecting between vein and artery is then thrown medially with its contained fat, glands, and lymphatics. Now two fingers of the hand can be gently insinuated between the medial surface of the psoas muscles and the vessels (Fig. 3). Keeping close against the pelvic wall they are pressed down to the pelvic floor and the whole mass of tissue including the main obturator gland is swept off the pelvic wall and displaced toward the uterus. With it has gone the obturator nerve which is easily hooked back with the fingers and laid against the pelvic wall. In the upper border of the mass the obliterated umbilical artery is identified, freed, and pulled upon to show the origin of the uterine artery, either from itself or as a separate branch of the parent trunk. At this moment any glands (usually small) around the origin of these vessels and the other branches of the internal iliac artery can be swept into the main mass together with the one which is constantly present in the bifurcation formed by the two main arteries. This principle of attack from the true periphery to the center, without in any way traversing the offending tissue, will be expounded again when we come to consider radical dissection of the groin.

Of course all this could be continued to any length, and all the anatomical features of the radical hysterectomy exposed in turn. But that is enough. It simply deals with some of the things I like to teach and demonstrate to my assistants and any onlookers whenever the opportunities arise.

Inversion of the Vagina Following Hysterectomy

The excuse for the introduction of this operation is that it exemplifies what may be called the anatomy of tissue recognition.

Most of the patients who present themselves with this crippling condition are over 50 years of age and the uterus has usually been removed for fibromyomas or functional bleeding in the menopausal years. Operative cures which aim at preserving a functioning vagina may be tried in the occasional case but the only method which offers a certain cure demands almost a complete removal of the vaginal walls and a thorough repair of the pelvic floor—not only the restoration of structures to their usual anatomical positions but even the union of tissues which do not normally lie in apposition. Most of the anterior vaginal wall is removed by raising a triangular flap whose apex is below the urethral orifice and whose base is somewhat in front of the vaginal vault scar (Fig. 4). On the sides of the inverted vagina lateral incisions are made from the angles

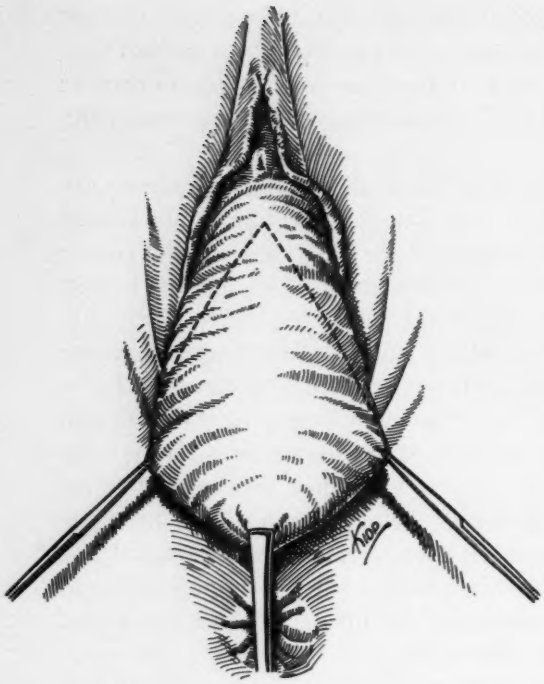


Fig. 4.

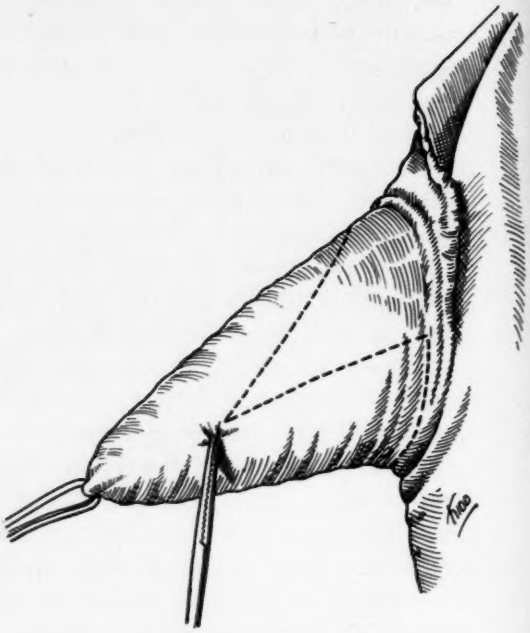


Fig. 5.

Figs. 4 and 5.—Inversion of the vagina showing suitable incisions for removal of vaginal skin.

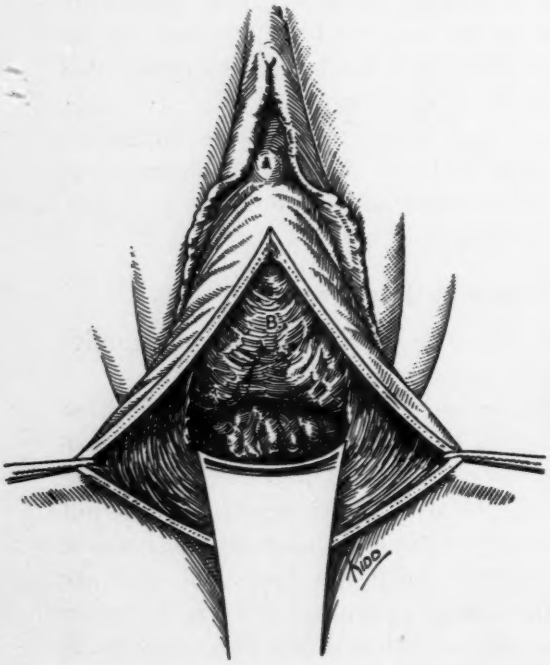


Fig. 6.

Fig. 7.

Fig. 6.—Bladder and tongue of peritoneum divested of vaginal skin. Rectum behind speculum.

Fig. 7.—Rectum, tongue of peritoneum, and levator masses divested of vaginal skin. Bladder behind speculum.

of the above flap to the junction of vaginal and vulvar skin. A final incision connects the ends of these around the junction of vagina and perineum (Fig. 5). It is through the last-mentioned incision that the rectovaginal space is entered, and the rectum is separated from the vaginal wall. The first dissection is the raising of an anterior vaginal flap from the bladder whose grayish fascial covering is maintained intact. True bladder musculature is met only in a small area quite close to the scar in the vaginal vault (Fig. 6). The nature of the tissue will now be seen to change; it is membranous and areas in it are almost translucent for it resembles what indeed it is, peritoneum. The posterior dissection is then begun by entering the rectovaginal space through the perineal part of the incision. First by sharp and then by blunt dissection with gauze-protected finger, the rectum is separated from the posterior vaginal wall (Fig. 7). This part of the dissection is confined mainly to the midline

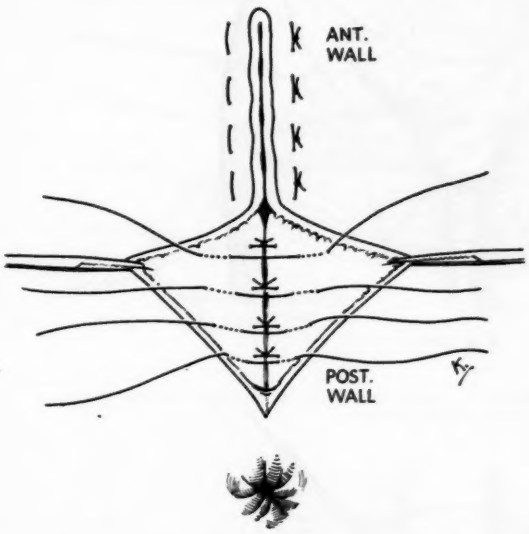


Fig. 8.

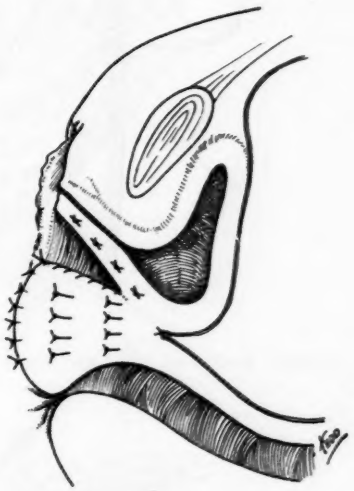


Fig. 9.

Figs. 8 and 9.—Coronal and sagittal diagrams of completed operation.

until at its apex extraperitoneal fat and the peritoneum are met once again and with finger behind and thumb in front these are found to be the only tissues (apart perhaps from some adherent omentum) intervening between the two digits. The peritoneal cavity is opened in finally freeing the old vaginal vault scar. The posterior wall is now raised from the pararectal tissues as far to the sides as our lateral incisions, the end result being an almost complete colpectomy. In the operative wound there are then seen from before backward (1) the bladder covered by its fascia, (2) a small area of true vesical muscle, (3) quite frequently a piece of projecting omentum, (4) true muscular wall of rectum from which a tongue of peritoneum will be hanging, and (5) in the extreme posterior part of the wound the lowermost portion of the rectal and anal walls covered by a certain amount of fascia. After closure of the peritoneum, a deep and extensive pelvic floor repair is carried out. The vesical part of this is accomplished by uniting the cut edges of the vaginal skin

by a series of strong mattress sutures which also include in their passage the deeper-lying fibrous and muscular tissues medial to the ischiopubic rami. The posterior part of the pelvic floor is built up in the classical way. The final result is a small vulvar orifice and a vagina reduced to a shallow cleft (Figs. 8 and 9). I have not seen a single recurrence following this procedure. Its

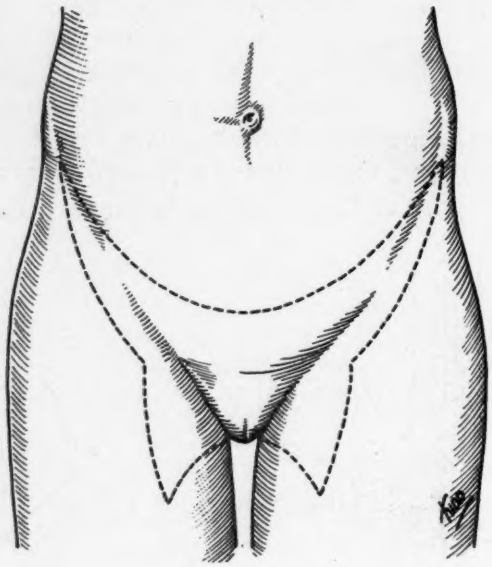
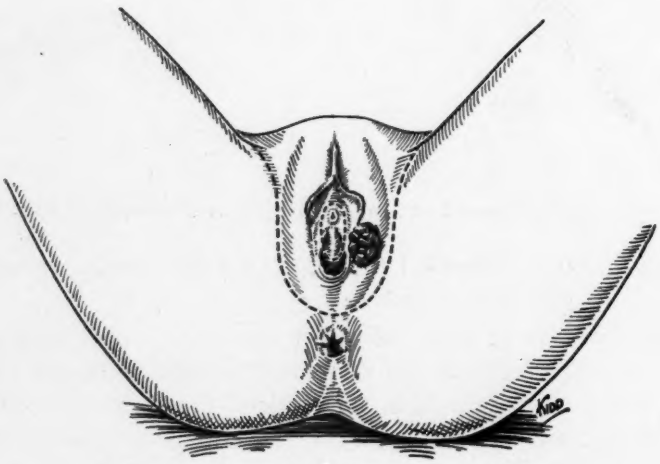


Fig. 10.



Figs. 10 and 11.—Showing routine incisions.

performance does not call for any intimate knowledge of topographical anatomy; it demands rather an easy familiarity with the lines of tissue cleavage and the ready recognition of peritoneum, omentum, bladder, and rectum when their relative dispositions have been considerably disturbed by the previous removal of one important pelvic organ and the complete inversion of another.

Cancer of the Vulva and Lymphadenectomy

There is perhaps no other tumor in the body which offers such magnificent anatomical possibilities for immediate, combined, and so complete an

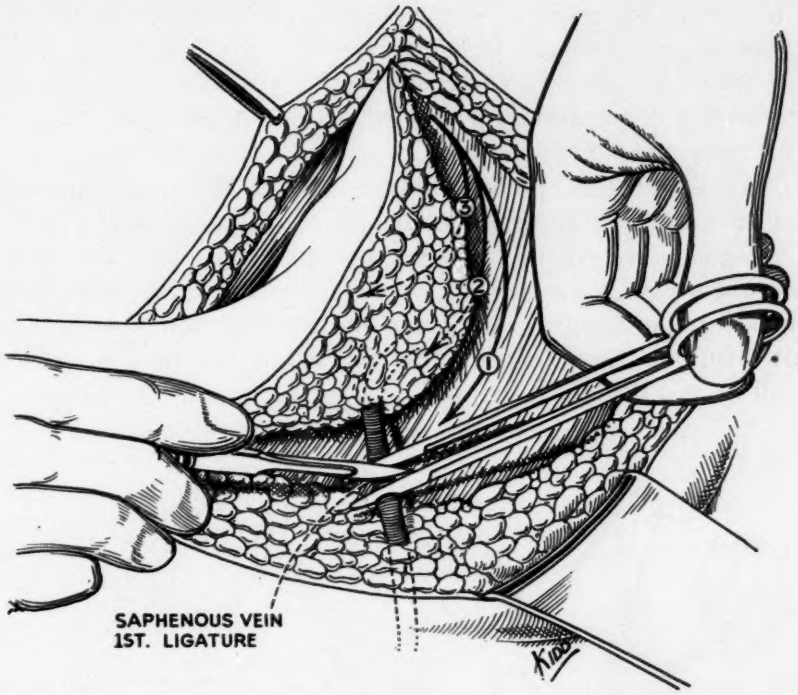


Fig. 12.—Left groin dissection showing lines of attack (*1*, *2*, and *3*) and first ligature of internal saphenous vein.

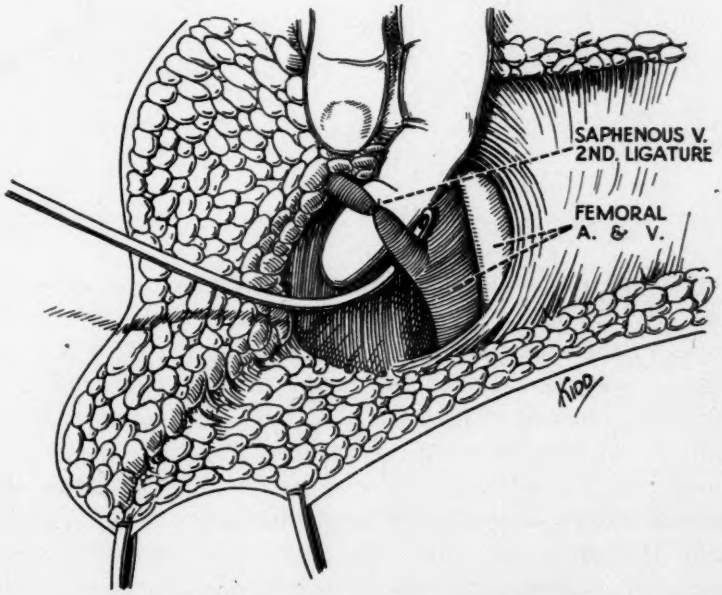


Fig. 13.—Second ligature of internal saphenous vein.

extirpation of the original lesion together with its primary and even secondary glandular stations. That all this can be easily realized and accomplished in keeping with the highest principles of a "block dissection" is due to the incisions planned by Stanley Way which include in one removal the vulva and the skin overlying the groins. The supreme advantage of taking the skin of the groins is, in my opinion, a technical one—it provides a source of firm traction which allows the operation to proceed with great ease and expedition and at no time makes it necessary for the operator to disturb the cohesion of the underlying fatty and glandular mass.

How then should this operation be taught? In this procedure it is better to state at once what structures are left behind. These are the aponeurosis of external oblique muscle and Poupart's ligament; the deep fascial coverings of the femoral nerve, the sartorius, iliopsoas, pectineus, adductor longus, and gracilis muscles; the femoral artery and the femoral vein; two stumps of the saphenous vein, one near the point where it enters Scarpa's triangle and one on the femoral vein itself.

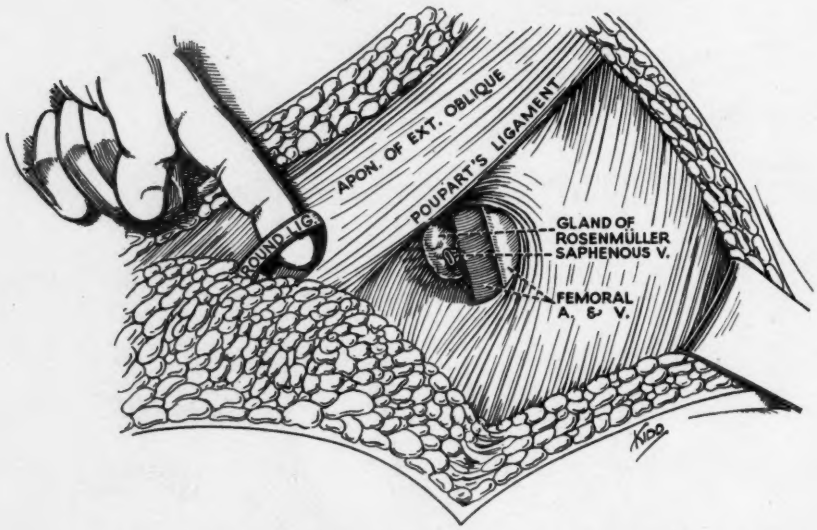


Fig. 14.—Exposure and division of third anchorage, the round ligament.

The groin incisions are first made on one side and the superficial vessels secured (Figs. 10 and 11). The whole of the upper incision is deepened to the aponeurosis of the external oblique and the outer half of the lower one to the deep fascia covering the muscles of the thigh. The outer angle of the skin is then firmly grasped (Fig. 12). By a combination of traction, touches with the point of the scalpel along the "thin white line," or by simple gauze stripping alone, the whole mass is raised medialward from the deep fascia, until the femoral artery is reached whose pulsations are first detected by the index finger of the left hand. Just internal to this are the femoral vein and the saphenous vein entering it. The attack is now directed downward and medially toward the apex of Scarpa's triangle. Here lying almost on the deep

fascia is the saphenous vein entering the operating field. It is secured, divided, and doubly ligated; thus the first anchorage of the mass is severed (Fig. 13). With further traction on the mass and returning to the femoral area the small

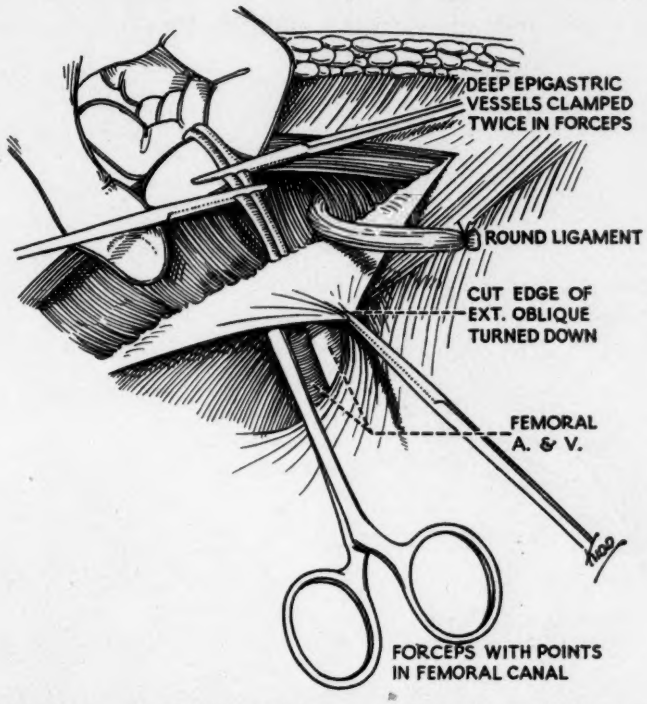


Fig. 15.—Preliminaries to pelvic brim dissection. Division and ligature of deep epigastric vessels and division laterally of internal oblique and transversus muscles.

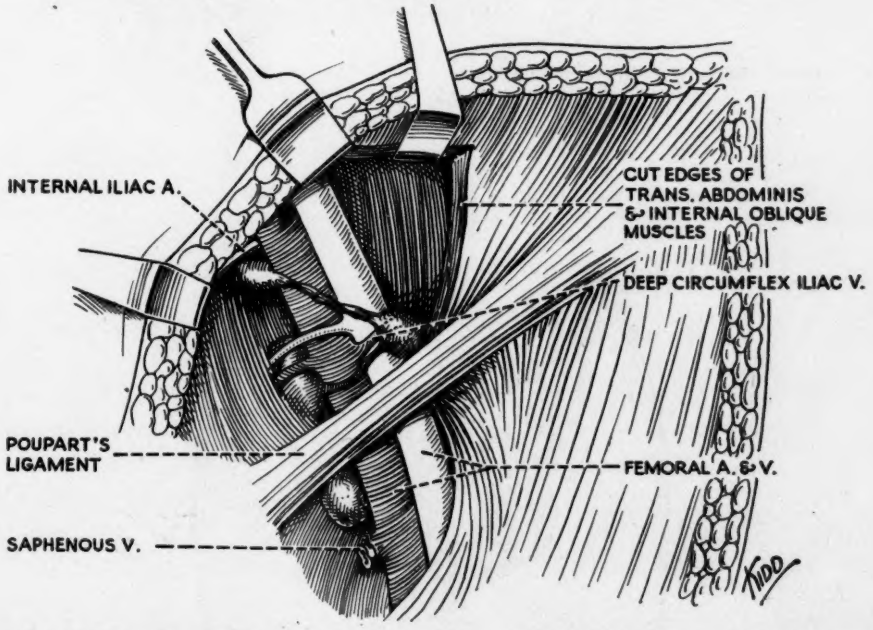


Fig. 16.—Showing part of the field exposed with a typical distribution of glands commonly found. Poupart's ligament is not divided.

arterial vessels proceeding from the anterior aspect of the parent trunk are secured, and just internal to these the saphenous where it enters the femoral vein; this, the second anchorage of the mass, is divided (Fig. 14). Now the dissection is diverted to a slightly higher area along the course of the inguinal canal. The external abdominal ring is identified and the round ligament se-

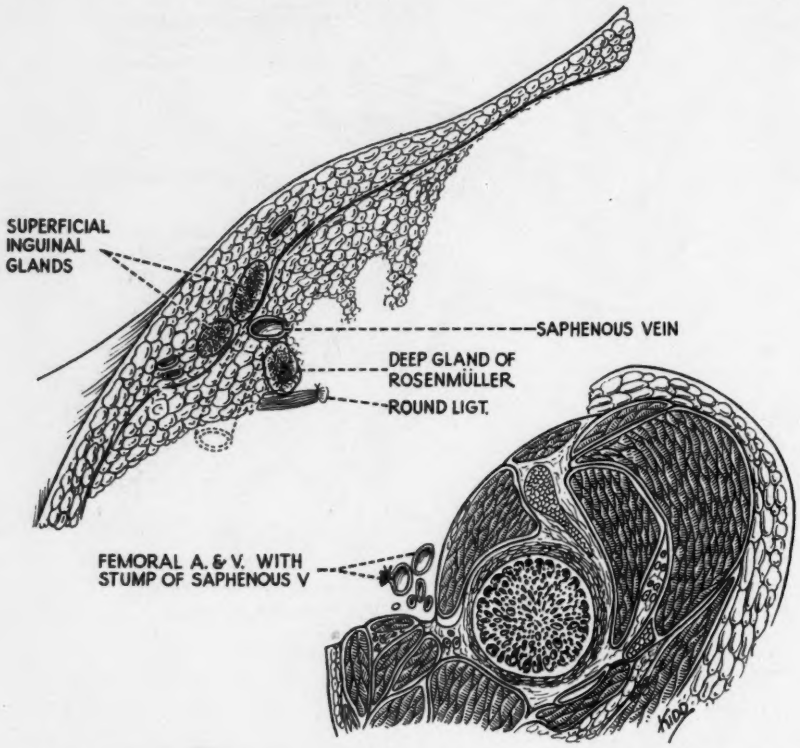


Fig. 17.—Groin dissection displayed in transverse section of thigh, showing what is removed and what is left behind.

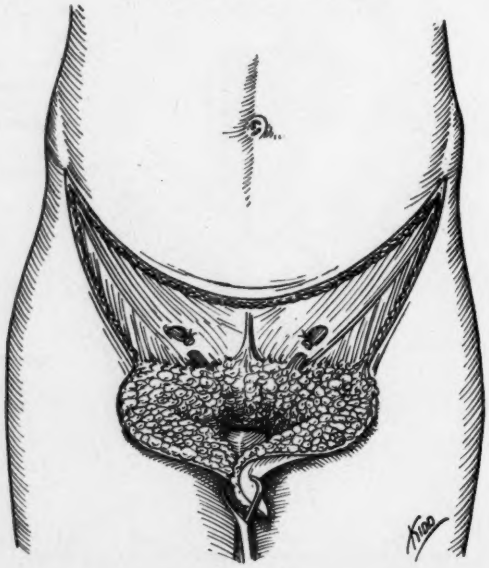


Fig. 18.—Dissected wings of tissue clipped together as preliminary to excision of vulva.

cured and sectioned, and so the third of the three main anchorages is now severed (Fig. 15). Just medial to the femoral vein the femoral canal is cleared of the fatty septum of Cloquet and the lymphatic gland of Rosenmüller (Fig. 16).

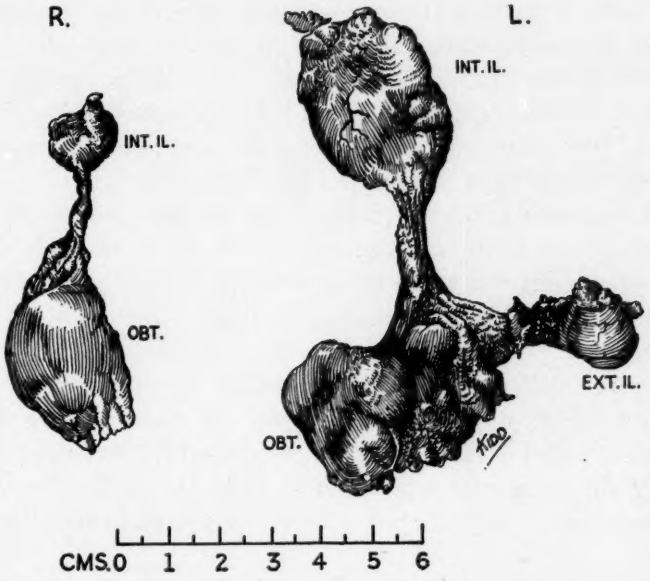


Fig. 19.—Right and left iliac glands with connecting lymphatics from actual case.

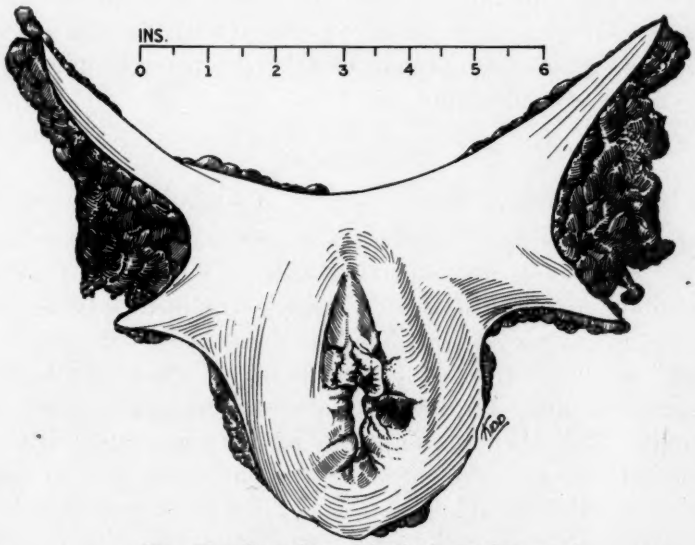


Fig. 20.—Drawing of typical specimen.

The operation is now directed to removal of the obturator and iliac group of glands. The inguinal canal is opened up, the round ligament retracted laterally and held vertically while the deep epigastric vessels just internal to the point where it enters the abdomen are identified and divided (Fig. 17). Two fingers of the left hand are then slipped laterally deep to the transversus

and internal oblique muscles. These are divided about one inch above Poupart's ligament (Fig. 18). The transversalis fascia and the peritoneum are swept inward and strongly retracted toward the midline. The iliac vessels and lateral pelvic wall are now exposed and lymphadenectomy can easily be carried to a point almost as high as the origin of the common iliac artery. Bleeding can arise only from the careless oversight of the presence in the field (1) of the deep circumflex vein (and artery) and (2) of an abnormal obturator artery and vein arising from the external iliac vessels, and passing over the pelvic brim to enter the obturator canal. These vessels pass over the medial surface of the "obturator" gland and are present much more often than the anatomical texts would have us believe (Fig. 19).

Poupart's ligament is never divided. As the film shows, the whole dissection is completely adequate without the introduction of such a step. If one wishes it, complete continuity can be maintained between the glandular masses of groins and pelvis. This gives an appearance of technical excellence but is not really necessary.

The technique differs from that described by Stanley Way in that the proximal 3 to 4 inches of the saphenous vein is always taken and Poupart's ligament is not divided. To attempt to save the former compels the operator to do the very thing against which Way (1948) himself advises, "to scratch about in an area which may contain cancer cells very neatly tied up in lymph nodes."

The first and only *inguinal* gland which the operator actually isolates as such is the one in the femoral canal. The whole specimen is fixed, spread out with skin downward, and the fatty and glandular mass thinly and repeatedly sliced (Fig. 20). In this way the slices are viewed like the pages of a book and the sectioned glands stand out clearly for macroscopic inspection and further microscopic examinations.

Conclusion

Five gynecological procedures have been illustrated by slides and films. Not one of them arises very frequently in the work of any one of us. This fact alone, however, is of special importance to our theme for it is essential that in any group of operations which are performed only occasionally and intermittently, the early cases in the series should be dealt with as thoroughly and effectively as the later ones. There is no reason why this should not be so if the beginner's first equipment is a sound comprehension of the fundamental anatomy. This then is one of our primary responsibilities—to encourage our juniors to acquire these basic principles early and to show them the rewards that will follow their acquisition. They are not only aids to technical and operative dexterity, but the only foundation upon which such surgical attainments can be securely built. "The potter and the clay endure." We are the surgical potters. Might we not then once again ask ourselves and each other the question according to St. Paul, "Hath not the potter power over the clay?"

THE FATE OF INTRAVENOUSLY INJECTED PLACENTAL EXTRACTS*†

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IN CASES of abruptio placentae occurring spontaneously in women or induced by trauma in pregnant rabbits,[1] there appears to be an escape of placental thromboplastic proteins into the maternal circulation. This results in what Schneider[2, 3] has termed "fibrin embolism" due to disseminated intravascular coagulation. A similar process may occur following crushing injuries, surgery of the lung, and other traumatic events, but the evidence in such instances is less well documented. Accompanying the more severe forms of abruptio placentae in women, a hemorrhagic diathesis may appear due to the acute depletion of circulating fibrinogen. Page, Fulton, and Glendening[4] were able to reproduce this syndrome in dogs by the intravenous infusion of human placental thromboplastin. During the course of those experiments it was noted that the thromboplastic activity of extracts prepared from samples of blood increased very little during or after the infusion, and it was apparent that the material disappeared from the blood stream with marked rapidity. The present experiments, utilizing thromboplastin labeled with radioactive iodine, were designed to study the fate and organ distribution of the material following its intravenous injection, and to study the relationship of its distribution to the development of fibrin emboli and other organic lesions.

Materials and Methods

Thromboplastin was prepared from human placentas and from rat lung by the process of differential centrifugation, as described in a previous publication.[5] The method of labeling this material was as follows: 0.8 ml. (3.2 mc.) of a carrier-free solution of I^{131} was added to 0.2 ml. of N/10 Lugol's solution and allowed to come to equilibrium for 3 minutes. This was added slowly and with constant stirring to 15 ml. of ice-cold thromboplastin solution. The mixture was then dialyzed repeatedly against ice-cold 2 per cent sodium chloride solution until the radioactivity of the dialysate was negligible. About 9 per cent of the total radioactivity was incorporated in the protein. The thromboplastic activity of the material, assayed by a modified two-stage procedure similar to that previously described,[6] decreased slightly as a result of this process, but no more so than control solutions treated in an identical manner in the absence of iodine. (The thromboplastic potency was roughly equivalent to a

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TABLE I. DISTRIBUTION OF I^{131} LABELED RAT LUNG THROMBOPLASTIN (RLT) AND RAT SERUM PROTEIN (S.P.) 15 MINUTES AFTER INTRAVENOUS INJECTION

GROUPS	NO. RATS	WHOLE BLOOD	HEART	KIDNEY	GASTRO-INTES-TINAL TRACT	LIVER	LUNGS	SKIN	SPLEEN	POOLED REMAINS
A. Percentage of Dose per Gram Observed ± Standard Deviation.—										
I. RLT to normal rats	10	1.28	1.25	0.94	0.50	4.54	2.75	0.38	1.74	0.32
		±0.41	±0.78	±0.34	±0.11	±0.79	±0.72	±0.11	±0.85	
II. RLT to heparinized rats	10	*0.93*	*0.45*	0.63	*0.68*	*6.47*	*0.82*	*0.53*	2.21	0.33
		±0.09	±0.06	±0.07	±0.28	±0.64	±0.10	±0.051	±0.95	
III. S.P. to normal rats	9	*5.58*	1.49	*2.18*	0.68	*2.17*	2.43	0.36	*1.07*	0.46
		±0.70	±0.27	±0.41	±0.08	±4.45	±0.61	±0.028	±0.14	
B. Percentage of Dose per Gram Corrected for Blood Content (See Text).—										
I. RLT to normal rats	10	1.28	0.97	0.51	0.42	4.11	2.26	0.37	1.51	0.26
II. RLT to heparinized rats	10	0.93	0.25	0.32	0.62	6.16	0.45	0.52	2.04	0.29
III. S.P. to normal rats	9	5.58	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.20

Italic figures indicate significant differences as explained in the text.

1/25 dilution of a reagent [Simplastin] commonly used in the Quick test.) In order to obtain comparable data with a protein solution free of thromboplastin, rat serum was subjected to high speed centrifugation (19,000g) to remove thromboplastic proteins, and the supernatant serum was labeled with I^{131} in the identical manner.

Rats of the Long-Evans strain, weighing between 150 and 200 grams, were lightly anesthetized with ether and the right jugular vein was exposed. The labeled solutions were injected slowly, using 0.5 ml. of the placenta or lung preparations and 1.0 ml. of the labeled serum. The dosages selected were those which could ordinarily be injected within 30 seconds without causing death of the animal. Larger quantities of the thromboplastic material were given by slower infusion when radioautographs were desired. Groups of animals were sacrificed at intervals of 5, 15, 30, 60, 120 minutes, and 16 hours in order to determine the best interval for further study. After periods of a half-hour, the increased uptake of I^{131} by the thyroid gland, together with the appearance of slight radioactivity in the urine, indicated a dissociation of the iodine from the protein. For this reason, the interval of 15 minutes was selected for more intensive study.

Immediately prior to sacrifice, blood was obtained by heart puncture for a measurement of circulating thromboplastin. The organs were then separated, weighed, and the radioactivity measured with a Geiger-Müller counter. The carcasses from each group were pooled, ground in a powdered meat grinder, and the radioactivity was determined on an aliquot portion. Activity values are expressed as percentage of dose administered for each gram of tissue under consideration.

In the first series of experiments, thromboplastin isolated from human placenta was used. In the last series, exemplified by the data reported below, rat lung thromboplastin was prepared in order to eliminate the possibility that the disposal of the injected placental material was influenced by its human origin. No essential differences were noted between the fates of the heterologous and homologous tissues.

The animals were divided into three groups. Groups I and II received intravenous thromboplastin as described above, the only difference being that Group II received 0.1 ml. (10 mg.) of heparin* intravenously immediately prior to the injection of the thromboplastin. This was done so that we could study the fate of the thromboplastin in the absence of intravascular coagulation. Group III received 1.0 ml. of the labeled rat serum intravenously.

Results

The distribution of the radioactivity in the various tissues of each of the three groups of animals is shown in Table I. The data presented were obtained from those animals sacrificed 15 minutes after injection of the labeled material, and are expressed as percentages of the total dose found in each gram of tissue. In the first half of the table (*A*), the observed data are given together with the standard deviation. In Group II, the italic figures indicate results which differ significantly from those of Group I; whereas in Group III, the italic figures indicate results which differ significantly from those of both Groups I and II.

Because the organs contained varying quantities of blood after their separation from the animal, it is possible that some of the observed differences might be due to the radioactivity of the blood remaining in each organ. The total blood volume of the Long-Evans strain of rat used in these studies has been measured repeatedly by the method of chromium-tagged red cells by two of us

*The authors wish to record their indebtedness to The Upjohn Company for supplying heparin solution containing 10,000 units per milliliter.

(K. S. and L. S.) and found to average 7 per cent. Based on the assumption that the soft tissues (i.e., excluding bone) contained the same amount of *extravascular* labeled serum protein per gram, and utilizing the mean weights for each organ or tissue, the amount of blood remaining in each organ or tissue was calculated. By subtracting the calculated amounts of radioactivity due to blood from the observed data, values were found which are illustrated in the second half of the table (*B*). These represent an approximation of the ability of each tissue to concentrate the labeled thromboplastin. No appreciable differences in ratios of distribution were found between the observed and the "corrected" data, except in the case of the kidney. In this organ, the high activity noted after injection of labeled serum is apparently due to the large amount of blood contained therein. This indicates that the concentration of thromboplastin by the liver, for example, is not a reflection of the contained blood.

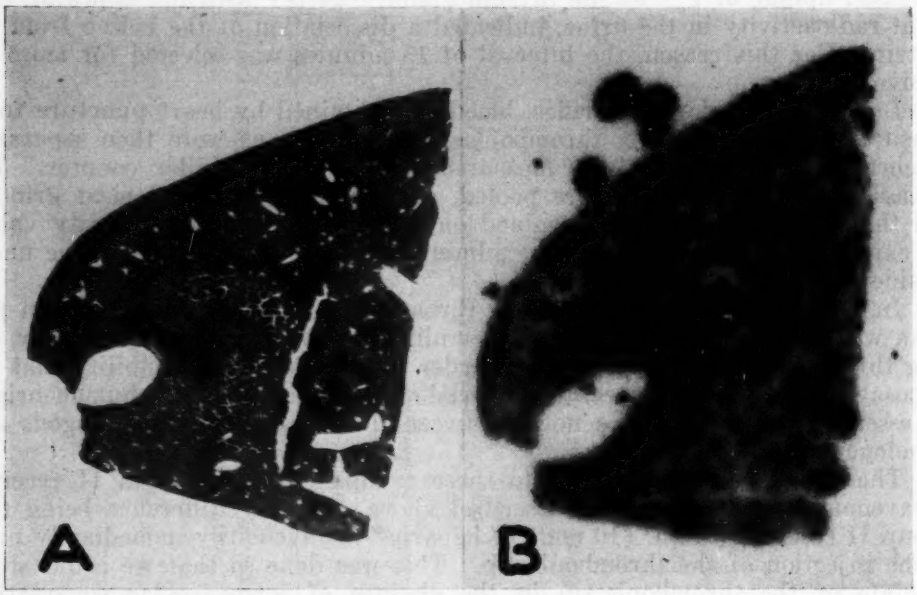

Fig. 1.—Liver from a rat injected intravenously with radioactive thromboplastin. *A*, Low-power photomicrograph. *B*, Radioautograph from adjacent section. (The solid black circles beyond the edge are deposits of fibrin which were washed off in preparing the stained section.)

In comparing the first two groups, i.e., the nonheparinized and the heparinized rats injected with thromboplastin, it will be noted that the heart and lungs removed significantly greater amounts of thromboplastin when the coagulation system was in operation. This might well be expected, since the material injected into the jugular vein passed first through the heart and lungs, and fibrin deposition occurred in both organs. As will be illustrated by an experiment performed in vitro, and described below, fibrin adsorbs almost half of the available thromboplastin during coagulation. This removal by the heart and lung left less material for distribution in other tissues, which accounts in part for the higher values noted in the liver, skin, spleen, and gastrointestinal tract of the heparinized animals. The surprising fact is that in both groups, taking organ weights into consideration, the liver removed from 41 to 47 per cent of all the material injected within 15 minutes.

Perhaps the most important effect of heparinization was to alter the nature of the thromboplastin distribution within the organ itself. Radioautographs

of the lungs, liver, spleen, and kidney revealed a very spotty distribution in the normal animals, each spot of light on the autograph corresponding with an area of fibrin deposition in the microscopic section. Following heparinization, the distribution of the thromboplastin was very diffuse, with no localizations noted. These differences, in the case of the liver, are illustrated in Figs. 1 and 2. It is possible that the reticuloendothelial system is responsible for the concentration of labeled thromboplastin in the liver of the heparinized animal.

In one experiment, an infusion of labeled placental thromboplastin was given into the femoral vein of a dog weighing 8 kilograms. During the infusion period of 60 minutes, the radioactivity of the blood rose steadily until at the end of the injection period the total volume of blood in the animal contained 35 per cent of the injected dose. Twenty minutes later, when the dog was sacrificed, this figure had fallen to 19 per cent, illustrating the rapidity of the

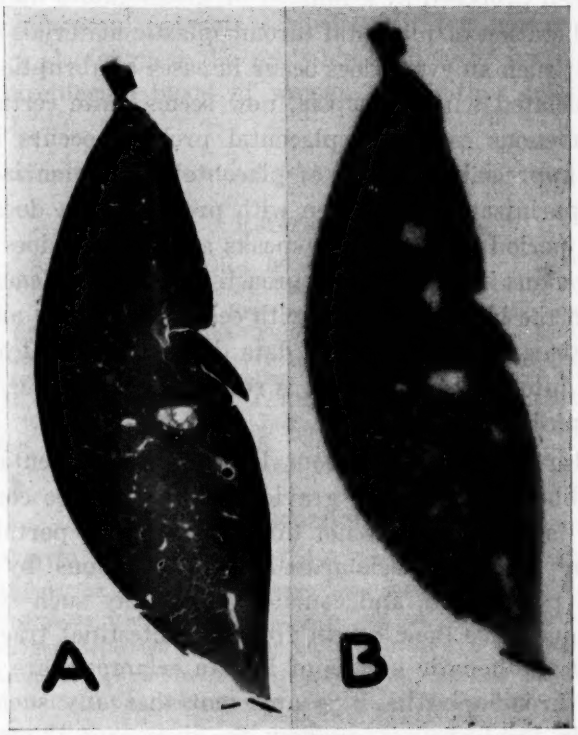

Fig. 2.—Liver from a heparinized rat injected intravenously with radioactive thromboplastin.
A, Low-power photomicrograph. *B*, Radioautograph from adjacent section.

removal. Of the remaining thromboplastin (i.e., 81 per cent of the total dose), 60 per cent was found in the liver, 15 per cent in the lungs, and 7 per cent in the spleen. Thus the distribution in the dog was similar to that observed in the rat. During the infusion, the clotting time of the dog's blood increased from 4 minutes to 27 minutes because of defibrination.

Experiments were also carried out in vitro to determine how much thromboplastin might be physically adsorbed to fibrin during the coagulation of agitated blood. Radioactive thromboplastin was added to oxalated human blood, the sample was recalcified and stirred with a group of small glass rods until fibrin formation was complete. The clot gathered by the glass rods was only

12 per cent of the sample by weight but contained 47 per cent of the radioactivity. In order to rule out the possibility that the thromboplastin was incorporated in the fibrin clot by virtue of its participation in the conversion of prothrombin to thrombin, the same experiment was performed, except that thrombin was added to the oxalated blood instead of calcium. Again, the clot removed was 12 per cent of the total weight and contained 46 per cent of the radioactivity. This would suggest that if enough thromboplastin is given intravenously to bring about complete defibrination in vivo, about half of the material would be incorporated in the disseminated fibrin deposits.

Comment

The results obtained in this study have certain clinical implications with respect to human eclampsia and abruptio placentae. Since the turn of the century, it has been proposed by a number of investigators that eclampsia might be caused by a liberation of placental thromboplastic materials into the maternal circulation. That such an event does occur in cases of abruptio placentae, which is sometimes associated with eclampsia, now seems quite certain. Whether an autogenous intravenous escape of placental proteins occurs in eclampsia unaccompanied by appreciable degrees of placental separation is a dubious point. The fact that heparinization of women with pre-eclampsia does not "cure" the syndrome over a period of three days speaks against, but does not disprove the concept.[7] The obvious investigative approach would be to demonstrate placental thromboplastin in the blood of women with eclampsia. Such an approach would probably be fruitless, since the present data demonstrate that any such material gaining entrance into the blood stream is removed by the liver and other organs with extreme rapidity.

The data also indicate that about half of any placental thromboplastin which might be liberated from the gravid uterus would be concentrated in the liver despite the fact that it does not directly enter the portal circulation. In 1929, Dieckmann[8] produced eclampsia-like liver lesions by injecting tissue extracts into the portal vein, and concluded that any such substances causing hepatic lesions must have their origin from the intestinal tract. While we are not claiming that the hepatic lesions of human eclampsia are caused by autogenous placental thromboplastin, it is apparent that any such material would be concentrated in focal areas throughout the liver even though it reached this organ by a circuitous route. We have produced hepatic lesions similar to those described by Dieckmann and by Schneider by infusing placental extracts into the femoral vein of dogs.

Summary

Considerable evidence has accumulated to indicate that placental thromboplastic proteins escape into the maternal circulation in cases of abruptio placentae, and possibly in some cases of eclampsia. In order to determine the fate of such autogenous extracts, thromboplastin prepared from human placenta or from rat lung was labeled with radioactive iodine and injected intravenously into groups of rats and into one dog.

The labeled material disappeared from the blood stream with considerable rapidity. It was found to be concentrated in various organs, but notably in the liver (in which almost half of the administered dose was found), lungs, and spleen. Radioautographs demonstrated a focal distribution which corresponded to deposits of fibrin. Experiments with human blood in vitro indicated that about half of any available thromboplastin is adsorbed to fibrin during the coagulation process. Heparinization of the animals prior to injection alters the pattern of organ distribution and abolishes the disseminated fibrin embolism with its associated concentration of thromboplastin. That the peculiar distribution is not due to the content of blood in each organ was demonstrated by comparing these data with those obtained after the intravenous injection of labeled serum proteins.

The results of these experiments emphasize the central role of the liver in concentrating placental extracts regardless of the portal of entry into the circulation. They also suggest the probable futility of searching for placental proteins in the circulating blood of women with either eclampsia or abruptio placentae.

We wish to acknowledge the technical assistance of Jane O'Connell.

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Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—The present study is an additional step in the study of the coagulation defects which have been demonstrated in some cases of abruptio placentae. This ingenious use of a measurable isotope adds information concerning the mechanism of fibrinogen depletion which the authors believe is the basis of the hemorrhagic state. The association of the radioactive thromboplastin material with the presence of fibrin deposits in the liver sufficient to account for approximately one-half of the injected thromboplastin represents an extremely important piece of evidence in the study of this condition. In addition, the rapidity with which the thromboplastic material is removed from the circulating blood is emphasized by the essayists. This explains the failure to demonstrate by study of the blood what the fundamental mechanism might be.

It is of interest that lesions similar to those produced in the liver of the experimental animal are seen in eclampsia. Whether one is justified in assuming a similar etiological relationship is yet to be demonstrated.

The fact that the hemorrhagic diathesis can be produced by the administration of thromboplastin and, as has been demonstrated by the authors and others, can be cured by the administration of fibrinogen in sufficient quantity would seem to be an adequate explanation. The present report further substantiates this concept and offers additional evidence of the mechanism by which it takes place.

FURTHER OBSERVATIONS ON SERUM CALCIUM AND PHOSPHORUS IN PREGNANCY*

ROBERT L. NEWMAN, KANSAS CITY, KAN.

(From the University of Kansas Medical Center)

THE importance of calcium in neuromuscular activity, blood clotting, and bone production has been emphasized by numerous observers. Blair-Bell and Hick were among the first to recognize its importance in uterine contractility. This importance was further emphasized by Danforth and Ivy with a complete failure in animals of uterine response to stimuli in the absence of calcium.

Previous work has established what is believed to be an "average normal" curve for serum calcium and phosphorus in pregnancy, labor, and the immediate puerperium. The disadvantages of using an "average" curve are appreciated but it was decided upon for its simplicity in demonstrating a trend well demonstrated by a "spot graph."

This curve is shown in Fig. 1, with the addition of an average of determinations performed on normal nonpregnant women for completeness. The curve shows a slight reduction in serum calcium and phosphorus during pregnancy, most pronounced in the seventh and eighth months, rising through the ninth month, labor, and the first ten days post partum to its original level. This rise is somewhat more abrupt in the case of serum phosphorus, although the significance of that fact, if any, is unknown.

For some time serum calcium has been recognized to consist of two components, diffusible and nondiffusible. The nondiffusible is supposedly bound to protein and is physiologically inert. It is from the diffusible fraction that the physiologically active calcium ion is obtained. Roughly 50 per cent of the total serum calcium is diffusible. The amount of diffusible calcium that is ionized has been a source of considerable argument and investigation. McLean and Hastings have demonstrated that all but a small fraction (less than 0.5 mg.) of the diffusible component is ionized and that the ionized calcium maintains a constant relationship to the total serum protein. Thus, knowing the total serum calcium in milligrams and the total serum protein in grams, the ionized calcium in milligrams can be calculated by means of a normogram as shown in Fig. 2.

Material and Methods

In an effort to alter the original curve of serum calcium and note any related clinical results, four types of calcium preparations were administered to four groups of prenatal patients who were followed during pregnancy, labor,

*Presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

and the puerperium with determinations of serum calcium, phosphorus, and total protein from which the amount of ionized calcium was determined by calculation, using the above method. As in the original work, only primiparas were used who were instructed in a pregnancy diet to include a quart of milk daily. The serum calcium was determined by the Clark-Collip modification

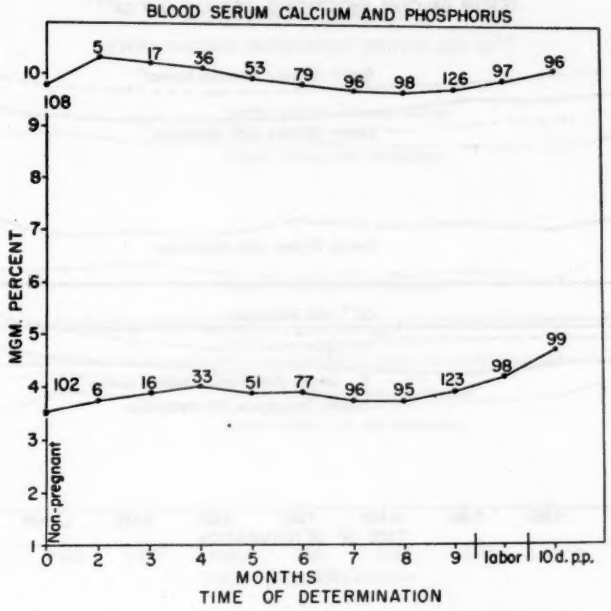

Fig. 1.

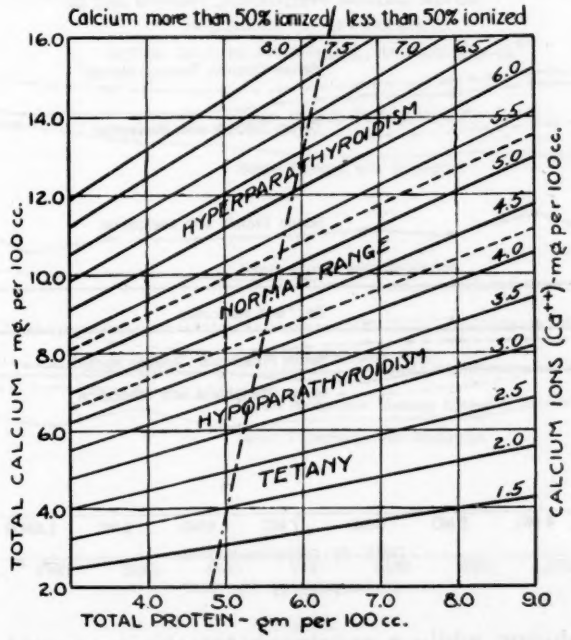
Calcium more than 50% ionized / less than 50% ionized
HYPERPARATHYROIDISM
NORMAL RANGE
HYPOPARATHYROIDISM
TETANY
TOTAL CALCIUM - mg. per 100 cc.
CALCIUM IONS (Ca++) - mg. per 100 cc.
TOTAL PROTEIN - gm per 100 cc.

Chart for calculation of Ca^{++} concentration from total protein and total calcium of serum or plasma.

Fig. 2.—(From McLean, F. C., and Hastings, A. B.: Am. J. M. Sc. 189: 601, 1935.)

of the Kramer-Tisdall method as in the original study. The serum total protein was determined by means of the Kagan proteinometer, a gravimetric method. In the original work a colorimetric method was used for the deter-

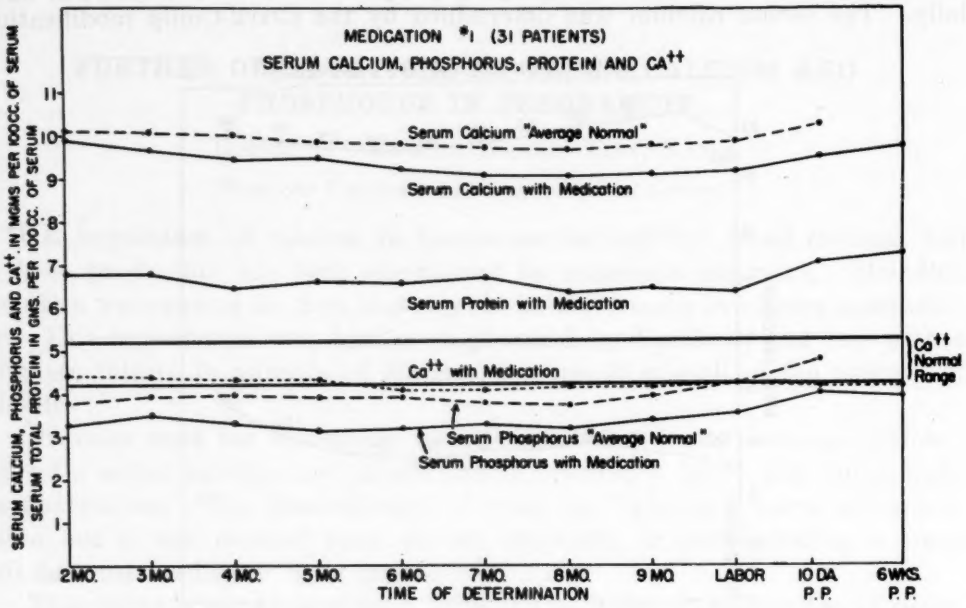

Fig. 3.

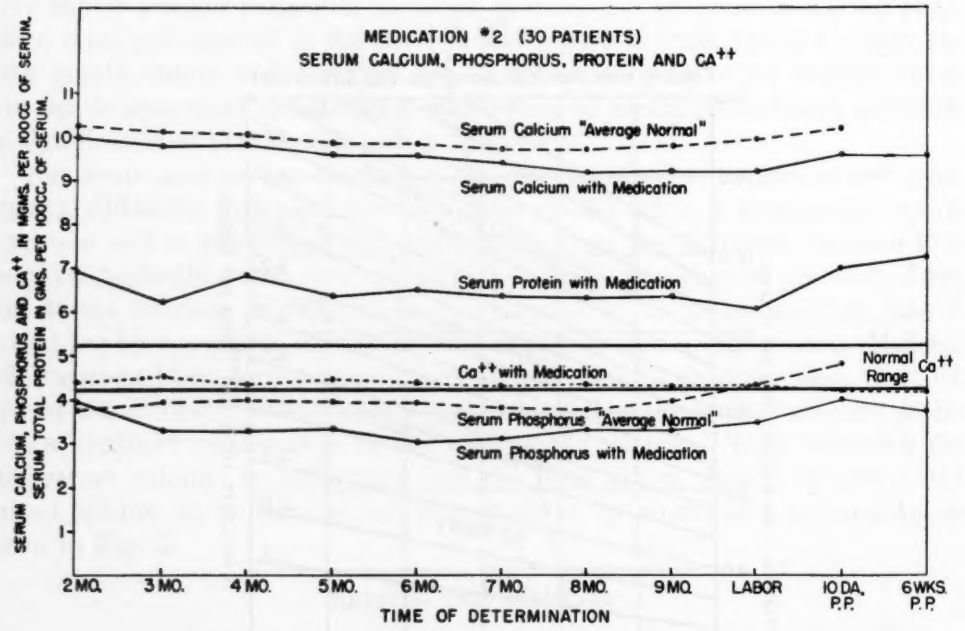

Fig. 4.

mination of phosphorus while a spectrophotometer was used in the present study for improved accuracy and speed.

Medication No. 1 supplied to the patient, in addition to her diet, 1.5 Gm. of calcium daily. The results with 31 patients are shown in Fig. 3. There

was no increase in serum calcium as a result of such therapy but a definite suggestion that it was decreased. The ionized calcium level ranged persistently at or below the lower range of "normal" (4.25 to 5.25 mg. per 100 c.c. of serum according to McLean and Hastings).

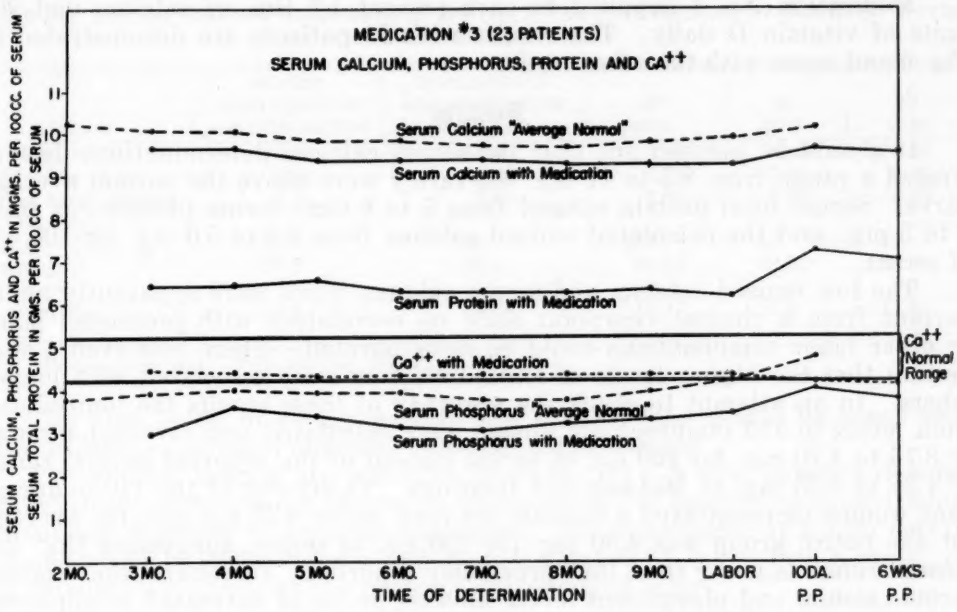
MEDICATION #3 (23 PATIENTS)
SERUM CALCIUM, PHOSPHORUS, PROTEIN AND CA++
SERUM CALCIUM, PHOSPHORUS AND CA++ IN MGMS. PER 100 CC. OF SERUM
SERUM TOTAL PROTEIN IN GMS. PER 100 CC. OF SERUM
Serum Calcium "Average Normal"
Serum Calcium with Medication
Serum Protein with Medication
Ca++ with Medication
Ca++ Normal Range
Serum Phosphorus "Average Normal"
Serum Phosphorus with Medication
2 MO. 3 MO. 4 MO. 5 MO. 6 MO. 7 MO. 8 MO. 9 MO. LABOR IODA. P.P. 6 WKS. P.P.
TIME OF DETERMINATION

Fig. 5.

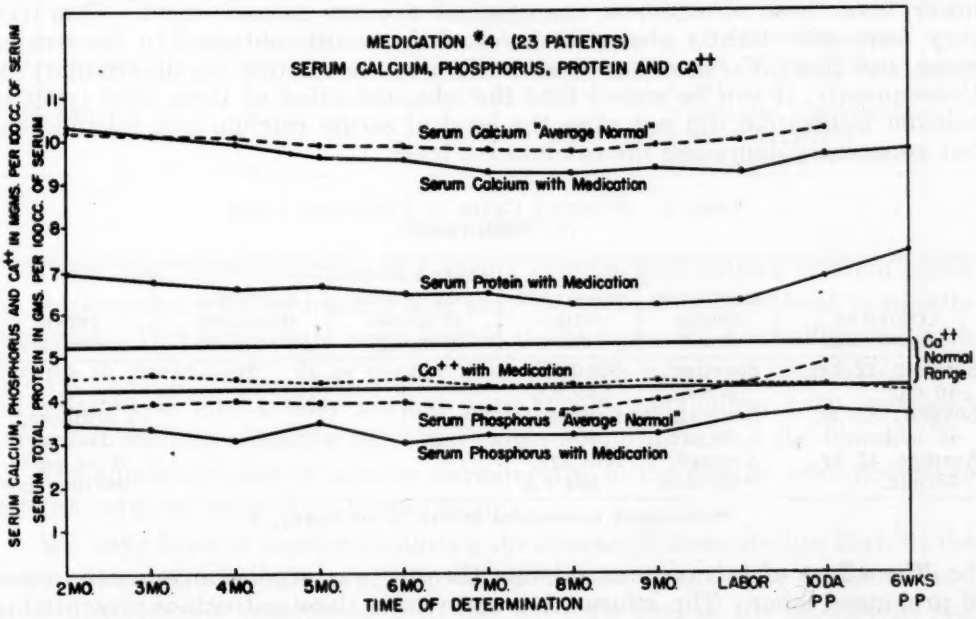
MEDICATION #4 (23 PATIENTS)
SERUM CALCIUM, PHOSPHORUS, PROTEIN AND CA++
SERUM CALCIUM, PHOSPHORUS AND CA++ IN MGMS. PER 100 CC. OF SERUM
SERUM TOTAL PROTEIN IN GMS. PER 100 CC. OF SERUM
Serum Calcium "Average Normal"
Serum Calcium with Medication
Serum Protein with Medication
Ca++ with Medication
Ca++ Normal Range
Serum Phosphorus "Average Normal"
Serum Phosphorus with Medication
2 MO. 3 MO. 4 MO. 5 MO. 6 MO. 7 MO. 8 MO. 9 MO. LABOR IODA. P P 6 WKS P P
TIME OF DETERMINATION

Fig. 6.

Medication No. 2 supplied to each patient approximately 2.2 Gm. of calcium and 1,500 units of vitamin D daily. The results with 30 patients are shown in Fig. 4. Again there was no elevation of serum calcium but a sug-

gestion of depression with the ionized calcium level ranging at or below the lower range of "normal."

Medication No. 3 supplied to each patient 2.6 Gm. of calcium and 600 units of vitamin D daily. The results with 23 patients are shown in Fig. 5 and are almost identical to those with medications No. 1 and No. 2.

Medication No. 4 supplied to each patient 1.7 Gm. of calcium and 900 units of vitamin D daily. The results with 23 patients are demonstrated in Fig. 6 and agree with the other results.

Results

It should be pointed out that the serum calcium determinations demonstrated a range from 8.5 to 11 mg. but rarely were above the normal average curve. Serum total protein ranged from 5 to 8 Gm., serum phosphorus from 3 to 5 mg., and the calculated ionized calcium from 3.5 to 5.0 mg. for 100 c.c. of serum.

The low ionized calcium and serum calcium levels were apparently unimportant from a clinical viewpoint since no correlation with prolonged labor or other labor complications could be demonstrated. There was even a suggestion that the higher levels of ionized calcium were associated with longer labors. In an attempt to check the accuracy of these results the ionized calcium levels in 110 nonpregnant women were calculated and revealed a range of 3.75 to 4.70 mg. for 100 c.c. of serum instead of the reported normal range of 4.25 to 5.25 mg. of McLean and Hastings. Thirty-one of the 110 nonpregnant women demonstrated a calcium ion level below 4.25 mg. and the average for the entire group was 4.30 mg. for 100 c.c. of serum, suggesting that the normal range is lower than that previously reported. To confirm the original serum calcium and phosphorus levels, another group of untreated primiparous patients was studied. In fifty patients, followed from the eighth month of pregnancy through labor and the immediate puerperium, the results were lower than those obtained in the original average normal curve. However, they were still slightly above the level of the results obtained in the treated cases, and this difference was most marked in the calcium ion determinations. Consequently, it can be stated that the administration of these four types of calcium medication did not raise the level of serum calcium and calcium ions but apparently depressed the calcium ion level.

TABLE I. NINETEEN CASES OF PROLONGED LABOR
(17 PRIMIPARAS)

LENGTH OF FIRST STAGE	LENGTH OF SECOND STAGE	BLOOD LOSS THIRD STAGE	CESAREAN SECTION (AFTER 43 HOURS OR MORE)	MATERNAL MORBIDITY (NO DEATHS)	FETAL MORTALITY
Shortest, 22 hr., 40 min.	Shortest, 3 min.	Smallest, 85 c.c.	3	10	4
Longest, 85 hr., 46 min.	Longest, 68 min.	Largest, 700 c.c.			(3 stillborn, 1 died on third postpartum day)
Average, 45 hr., 30 min.	Average, 32 min.	Average, 294 c.c.			

Subsequent uneventful labors (1 or more), 8

The effect of intravenous calcium therapy was studied in nineteen cases of prolonged labor. The information concerning these patients is presented in Table I. Only one of these patients had a labor less than 24 hours long and this one is included since progress stopped at 8 cm. dilatation for 8 hours. This seemed a favorable situation for calcium therapy. One Gm. of calcium gluconate, supplying approximately 100 mg. of ionized calcium, in 500 c.c. of 5 per cent glucose in distilled water was administered intravenously to each of

these patients over a period of thirty minutes. Blood determinations were made prior to administration of the medication and every thirty minutes thereafter for two hours. The results of these determinations are recorded in Table II.

TABLE II. 1.0 GM. CALCIUM GLUCONATE IN 500 C.C. 5 PER CENT GLUCOSE IN DISTILLED WATER (GIVEN IN 30 MINUTES)

AVERAGE	BEFORE INTRAVENOUS ADMINISTRATION	INTRAVENOUS ADMINISTRATION FINISHED	30 MIN.	60 MIN.	90 MIN.
Ca (mg. %)	10.46	10.63	10.60	10.48	10.68
Ca++ (mg. %)	5.03	5.26	5.18	5.04	5.19
Serum total protein (Gm. %)	6.11	5.67	5.86	6.03	5.99
Glucose* (mg. %)	71	132	101	83	77
Hematocrit (c.c. %)	39.3	38.1	38.05	39.2	38.1
Hemoglobin (Gm. %)	12.1	10.98	11.17	11.9	11.6

*Two curves, flat. Two curves, diabetes.

The high levels of serum calcium and calcium ions should be noted and there is little evidence of chemical response to the therapy.

The clinical results are recorded in Table III. A few patients demonstrated slight improvement of uterine contractions but essentially none demonstrated any increase in cervical dilatation. The importance of a firm cervix is emphasized by these figures and that fact must be taken into account in any satisfactory attack on the problem of prolonged labor.

TABLE III. NINETEEN CASES PROLONGED LABOR

CERVICAL CONSISTENCY	CERVICAL LACERATIONS (SEVERE)	INCREASED CERVICAL DILATATION AFTER CALCIUM	UTERINE RESPONSE TO CALCIUM
Firm, 14 Normal, 5	8	1 (2 to 4 cm.)	3 improved 3 doubtful improvement 1 marked (tetany) [Ca followed by pitocin]

Conclusions

These results demonstrate that serum calcium and ionized calcium levels are not elevated with medication and that the ionized calcium level is slightly depressed. This fact would seem to cast doubt upon the advisability of such therapy in pregnancy. It is conceivable that the administration of calcium and vitamin D might alter normal parathyroid metabolism with increased storage of calcium affecting the usual calcium equilibrium in the blood.

The administration of calcium parenterally, in the dosage used, proved to be of no value in cases of prolonged labor.

We have become convinced during the course of these studies that, at the present state of our knowledge, the determination of one or two of the blood constituents cannot possibly give us any accurate idea of the alterations and changes that occur. Consequently, these studies are being enlarged to cover a much broader range of these constituents.

I wish to thank Mrs. Emily Haas for her very able assistance and the Eli Lilly Company for supplying one of the drugs used in this study.

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Newman, R. L.: Am. J. Obst. & Gynec. 53: 817, 1947.

Discussion

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—Only when dietary deficiencies are extreme and the resultant pathologic changes glaring can one draw valid conclusions about malnutrition. In the course of six years in China it was my privilege to see many pregnant women suffering from osteomalacia. Here are some of the things which osteomalacia teaches us:

1. Patients with osteomalacia are not prone to uterine inertia. On the other hand, their uteri sometimes function so vigorously that they rupture. This is in keeping with the findings of Dr. Newman that intravenous calcium is of no value in uterine inertia. Our own experience has been similar.

2. Patients with osteomalacia do not have eclampsia with greater frequency than nonosteomalacic gravidas. This is mentioned because low serum and tissue calcium has been suggested as a possible cause of the toxemias.

3. The fetus never suffers from the disease. Cases of fetal osteomalacia or fetal rickets are practically unknown.

4. Osteomalacia occurs only in pregnant women and abates between pregnancies.

The fact that the baby gets all of the calcium he needs, coupled with the fact that osteomalacia occurs only in pregnancy, means that the growing fetus imposes a strain on the maternal calcium. If calcium intake is practically zero, as it is in certain areas of North China, and if gravidas get little or no sunshine as obtains in those regions, bony malleability tends to develop. This drain on maternal calcium by the fetus has resulted in the recommendation years and years ago that pregnant women increase their milk intake. This recommendation has been extended to include medicinal calcium in the form of pills or capsules. Dr. Newman now comes before us and doubts the advisability of medicinal calcium in pregnancy. Now, these days, to doubt the advisability of giving pregnant women calcium pills or capsules is a good deal like doubting the advisability of virtue or patriotism or washing your teeth regularly.

Nevertheless, there are several reasons for believing, quite apart from the beautiful and convincing study that he has presented, that Dr. Newman's viewpoint is correct. These reasons are as follows: (1) No proved case of osteomalacia has ever been reported in the United States; and it would seem unlikely that minor degrees of calcium lack are common in the United States if no full-blown case of calcium deficiency is on record. (2) The symptoms which some observers have attributed to mild osteomalacia are muscular aches and cramps. The pain of osteomalacia is essentially bone pain. (3) Most important, however, particularly from the viewpoint of practical, everyday obstetrics, is the fact that emphasis upon calcium pills and capsules, emphasis on minerals and vitamins in the form of pills and capsules which may or may not be absorbed, serves inevitably to de-emphasize the importance of calcium, minerals, and vitamins from natural sources, such as milk, etc., which are absorbed and which are efficacious. This glib acceptance of vitamins and minerals in the form of pills and capsules is developing more and more and it would seem to be one of the shortcomings of modern prenatal care. In view of all these facts, Dr. Newman's contention based on an exceedingly meticulous and well-documented study merits our serious thoughts.

DR. H. HUDNALL WARE, JR., Richmond, Va.—The number of patients studied by Dr. Newman certainly seems to be sufficient to justify his conclusion that the normal calcium ion level may be lower than the average normal previously reported.

The fact that in four groups of patients treated with different types of calcium preparations there was no increase in the ionized calcium level, but an average below the normal level was found, necessitates a re-evaluation of the use of calcium as a supplement in the diet of a pregnant woman.

I have advised the daily use of 15 to 30 grains of calcium with vitamin D in our prenatal patients almost routinely after the fourth month of pregnancy. Several of my dental friends have thought that this medication has reduced the incidence of dental complications. In many patients the dentists have reported the teeth in better condition during pregnancy than they were prior to conception.

Dr. Newman's findings cause us to question the accuracy of these impressions. It also seems possible that the regulation of the patient's diet may be an important factor in improving the patient's calcium level.

The group of patients with prolonged labors interests me particularly. The essayist's studies prove that the administration of calcium and increase in the blood calcium did not improve the uterine contractions or shorten the duration of labor in his cases.

I am sure we all agree with Dr. Newman when he says that, at the present state of our knowledge, the determination of one or two of the blood constituents cannot possibly give us an accurate idea of the alterations and changes which occur in a patient.

DR. ERNEST W. PAGE, San Francisco, Calif.—There might be an alternative explanation for Dr. Newman's findings relative to the question of calcium supplements. We became interested in this subject in relation to the cause of muscle tetany or leg cramps in pregnancy. In a report which is yet to be published, we measured the diffusible calcium and phosphorus levels of the blood on ten normal pregnant women during different dietary periods. On a high milk intake, the mean diffusible calcium concentration was 5.6 mg. per cent, whereas on a low milk intake for five days the concentration rose to 6.4 mg. per cent. Corresponding with this, the phosphorus level fell from 4.3 to 3.6 mg. per cent. Leg cramps produced by dicalcium phosphate disappeared when calcium lactate was substituted. This suggested the hypothesis that the chief factor causing a fall of the ionized calcium level in pregnant women is the phosphorus content of the diet.

Dr. Newman tells me that all of the calcium supplements used in his study consisted of dicalcium phosphate. Based upon our observations, we believe that calcium supplements in pregnancy may be desirable provided they do not contain phosphate. One can remove phosphates from the gastrointestinal tract by the administration of aluminum hydroxide gel. In 44 pregnant women complaining of leg cramps, the administration of aluminum hydroxide gel alone resulted in a prompt relief of the symptom in 32 and improvement in 9. For example, in one subject who had been drinking two quarts of milk daily in addition to taking dicalcium phosphate, the measured diffusible calcium concentration of the serum was only 3.2 mg. per cent, which is well within the tetany range. After substituting a calcium supplement free of phosphorus and taking three or four tablets of Amphojel or Creamalin with each meal, the calcium level of her blood rose to normal limits and the muscle tetany disappeared. I am suggesting, therefore, that the fall in total calcium observed by Dr. Newman might be due to his choice of the calcium supplement, a choice which we have all so commonly made in the past.

DR. NEWMAN (Closing).—The original purpose of the study was not that of proving the advisability of using calcium medication. The purpose was to try to alter our original curve to see what happened and we were unable to do so and it seemed to work in reverse. The economic implications mentioned by Dr. Eastman are appreciated since the medication used in this study was purchased individually by us and we can certainly testify to that particular part of the problem. Dr. Page's point about the combination of calcium and phosphorus in dicalcium phosphate is a very interesting one to me and I must admit that every one of these medications that we have utilized did have the calcium in the form of dicalcium phosphate. Just how much effect that had, I do not know—perhaps in further studies we will be able to determine more accurately.

ACUTE RENAL FAILURE IN OBSTETRICS AND GYNECOLOGY*

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ACUTE renal failure in obstetrical patients suffering from abruptio placentae, eclampsia, prolonged labor, sepsis and hemorrhage, has been recognized for some years.[1-4] The similarity of the clinical course of these patients to that found in war wounds with shock,[5] crush injuries, exogenous poisons, and burns has been noted by many writers. The treatment has varied over the years.

In order to assess the significance of this condition and determine, if possible, the most satisfactory method of management, case records for a ten-year period, 1942 to 1952, have been reviewed. In this interval, only 39 cases were found. Sixteen of these were neither obstetrical nor gynecological and were excluded from this study. Of the remaining 23, 15 were seen in the Toronto General Hospital; 8 were from the Toronto Western and Grace hospitals. In many of these, one of us was intimately involved as consultant or attending physician. All patients presented the common finding of transitory or prolonged anuria or oliguria with evidence of nitrogen retention if the condition persisted beyond twenty-four hours.

Summary of Clinical Features

Age Incidence.—This varied from 21 to 45 years. In the cases in which the patient's age was recorded, 11 were in the twenties, 5 in the thirties, and 3 in the forties.

Etiology.—A variety of predisposing factors were present in the patients studied (Table I).

TABLE I. GROUP CLASSIFICATION

Group 1.—		
A. Abruptio placentae		9
B. Eclampsia		2
Group 2.—Sepsis		8
Abortion	6	
Labor	2	
Group 3.—Miscellaneous		
A. Postoperative shock		1
B. Incompatible blood transfusion and shock		1
C. Sulfonamide intoxication		1
D. Periarteritis nodosa		1
Total		23

*Presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

The precipitating factor was not always a single one of those noted above. In the abruptio placentae and eclampsia group which made up almost 50 per cent of the cases, toxemia, hemorrhage, and shock were present in a substantial number. Similarly, in the septic cases multiple etiological factors were evident. That which seemed of greatest significance has been designated as the primary cause.

Oliguria and Anuria in Relationship to Mortality

Abruptio and Eclampsia Group (11 Cases, 2 Deaths).—Five patients had complete anuria for a minimum of one and a maximum of two days followed by oliguria for one to eleven days. The average duration was five days. Two of the patients with anuria died.

Sepsis Group (8 Cases, 2 Deaths).—One patient had complete anuria till death four days after admission. In the remainder, oliguria persisted for three to fourteen days, the average being seven days.

Miscellaneous Group (4 Cases, 3 Deaths).—None suffered from anuria. Oliguria was present in all 4 cases for periods of one to seventeen days. In the patient who survived of this group, diuresis occurred on the fourth day.

TABLE II. RELATIONSHIP OF ANURIA AND OLIGURIA TO MORTALITY

	ANURIA			OLIGURIA		
GROUP	NO. OF CASES	DURATION (DAYS)	MORTALITY	NO. OF CASES	DURATION (DAYS)	MORTALITY 0
Abruptio and eclampsia	5	1-2	2 (renal failure)	6	1-11	
Sepsis	1	4	1 (renal failure)	7	3-10	1 (sepsis and renal failure)
Miscellaneous				4	3-17	2 (renal failure) 1 (periarteritis nodosa)
Total	6		3	17		4

Mortality.—In this series of 23 cases there were 7 deaths. These were distributed as follows: 2 in the abruptio group, 2 in the septic group, and 3 in the miscellaneous group. The shortest duration of life after the onset of acute renal failure was two days, the longest seventeen, and the average nine. In cases where death occurred within four days of the onset of renal failure, the initial injury or etiological factor, rather than renal failure, was the primary cause of the fatal outcome.

Onset of Diuresis.—In those patients who survived, the onset of diuresis occurred at varying intervals. In the abruptio and eclampsia group, the minimum was two days, the maximum twelve days, and the average six days. In the septic group, the minimum was five days, the maximum fifteen days, and the average ten days. In the sole survivor of the miscellaneous group, the onset of diuresis occurred on the fourth day.

TABLE III. DAY OF ONSET OF DIURESIS IN CASES OF RECOVERY

ETIOLOGY	MINIMUM	MAXIMUM	AVERAGE
All cases	2	15	5
Abruptio and eclampsia	2	12	6
Sepsis	5	15	10
Miscellaneous	4	4	4

Period of Survival in Fatal Cases According to Phase of Renal Function.—Transient, but not sustained, improvement in urinary output occurred in 2

of the fatal cases. Adequate diuresis was present in one patient who succumbed on the thirteenth day to hypopotassemia, hepatitis, and intestinal ulceration. The remaining 4 exhibited acute or gradual failure of urinary function. If one accepts the statement that the time of onset of diuresis is directly proportional to the severity of the renal lesion, then 8 of the patients who recovered had serious renal injury because in these 8 cases diuresis did not occur until eight to fifteen days had elapsed. In 6 of these cases the nonprotein nitrogen ranged between 115 and 227 mg. per cent. Three of these were treated by dialysis because they appeared to be deteriorating rapidly. It is pointed out, however, that 5 patients with equally long delay in the onset of diuresis and equally high levels of nonprotein nitrogen recovered without dialysis.

TABLE IV. PERIOD OF SURVIVAL IN FATAL CASES ACCORDING TO PHASE OF RENAL FUNCTION

PHASE	NUMBER	SURVIVAL
Complete anuria	2	4 days
Oliguria	2	7-8 days
Oliguria*	2	12-17 days
Diuresis	1	13 days

*Intestinal dialysis or artificial kidney.

Shock and Blood Pressure

Any patient was arbitrarily considered to be in shock who had a systolic blood pressure reading below 80 mm. of mercury. Relative shock was present in some of the abruptio and eclampsia patients whose pressure was recorded prior to the onset of anuria. Three of the 11 patients in this group had systolic pressures below 80 for at least 2 hours. As some of the patients were admitted some time after the onset of symptoms, it was impossible to estimate accurately the incidence of shock in this group. The great majority of the survivors maintained some hypertension throughout the greater part of their period of hospitalization. In the fatal cases, this was observed until the terminal phase of the illness. In the septic group, 4 had demonstrable shock in hospital. Again, it was impossible to determine its incidence in the remainder because of delay in admission to hospital. In all of the miscellaneous cases, shock was evident and played some part in the onset of the condition in the 3 fatal cases.

Urinary Findings

In the abruptio placentae and eclampsia group, gross blood was present in 4; microscopic blood and/or albumin in 6; and in 1, no record of early urinalysis was made. In the survivors, the specific gravity was low and fixed for the greater part of their stay in hospital. There was no mortality associated with the presence of gross blood in the urine. The presence of cellular and granular casts was noted in several cases though the presence of heme casts was not recorded in any instance, possibly through failure to recognize them.

Gross blood was present in 2 of the septic cases, microscopic blood in 3, and heme casts in 1. One of the patients with gross blood succumbed but no evidence of cortical necrosis was found at postmortem.

Of 3 fatal cases in the miscellaneous group, there was gross hematuria in 2. Two of these cases came to autopsy. Cortical necrosis was present in the one without gross blood in the urine and not in the other where this finding had been noted.

Blood Chemistry

In all cases in which the renal failure persisted for more than two days there was an increase in nitrogen retention. In the abruptio placentae and

eclamptic patients this varied from a minimum of 73 to 227 mg. per cent. In the fatal cases, the maximum recorded was 214 and in the nonfatal cases, 227 mg. per cent.

In the septic cases the minimum recorded was 75 and the maximum 217 mg. per cent. In the fatal cases the minimum was 130, the maximum 205 mg. per cent. The minimum in nonfatal cases was 75 and the maximum 217 mg. per cent. In the miscellaneous group the minimum was 144, the maximum 300 mg. per cent, the lower figure being found in the sole survivor in this group. Alterations in carbon dioxide combining power, chlorides, and potassium levels were present but controlled by therapy in all but one of the cases seen in recent years. This patient died in spite of adequate diuresis and apparently satisfactory control of the potassium level.

TABLE V. NONPROTEIN NITROGEN ESTIMATIONS

ETIOLOGY	MINIMUM	MAXIMUM
Abruptio placentae and eclampsia, fatal	206	214
Abruptio placentae and eclampsia, nonfatal	75	227
Sepsis, fatal	130	205
Sepsis, nonfatal	75	217
Miscellaneous, fatal	160	300
Miscellaneous, nonfatal		144

Treatment

A variety of therapeutic measures were employed singly or in combination in the management of these patients. Decapsulation of the kidney was performed once only, in a fatal case. Intestinal dialysis was used in 2 with 1 recovery; the artificial kidney in 2 with 1 recovery; sympathetic block and caudal anesthesia in 2 cases without apparent effect on renal function; peritoneal dialysis in 1 case with recovery; transplantation of kidneys in 1 fatal case; blood transfusion initially or during the course of treatment in 13 instances; balanced fluids in 18, and excess fluids in 3 patients, 2 of whom died partially as a result of overtreatment.

TABLE VI. METHODS OF TREATMENT

TREATMENT	CASES
Decapsulation of kidney	1
Peritoneal dialysis	1
Transplantation of kidneys	1
Sympathetic block or caudal anesthesia	2
Intestinal dialysis	2
Artificial kidney	2
Excess fluids	3
Blood transfusion	13
Balanced fluids	18

Pathology

Partial or complete postmortem examinations were done in 6 of the 7 fatal cases. The pathological picture varied from focal cortical necrosis in one instance to a variety of lesions all indicative of nephrosis as the outstanding feature. The distribution of the lesions varied in intensity and degree in different parts of the nephron. Two presented findings most marked in the lower nephron. Focal collections of lymphocytes were present in most instances in the medulla. In those with longer survival periods there was evidence of early attempts at tubular regeneration. These findings are similar

to those of Allen,[6] Smith,[7] Oliver,[8] O'Donnell,[9] and MacGillivray.[10] They suggest that the whole nephron rather than the lower nephron may be involved in patients suffering from acute renal failure.

Comment

From this study, hemorrhage, shock, trauma, prolonged labor, sepsis, and the administration of excessive amounts of sulfonamides seem to have been the precipitating causes of the development of acute renal failure. These have been reported before. Our findings in regard to the relationship of concealed and revealed hemorrhage in the abruptio placentae cases do not suggest a greater association of acute renal failure with the concealed type of hemorrhage as 6 were combined, 2 concealed, and 1 was entirely revealed. In this respect, we have been unable to corroborate Young's observation of the relationship of this clinical entity to that of concealed accidental hemorrhage. It is of interest to note that MacGillivray, and Duff and More[12] observed the occurrence of cortical necrosis in cases of revealed abruptio placentae and placenta previa, in contrast to Young's findings.

Shock and trauma due to prolonged labor, mismanagement, and sepsis formed the next largest group. The necessity of preventing these factors from becoming operative is noted. Should they occur, their prompt correction is imperative. Otherwise, the acute renal injury may be the decisive element in determining the outcome. Meticulous blood grouping and the rational use of sulfonamides in therapy will almost eliminate two other major causes of tragedy.

The prompt replacement of blood loss in all obstetric hemorrhage has been emphasized in recent years. It has an obvious and hackneyed air but, in spite of this, its importance is still unrealized by many obstetricians. This is particularly true in the management of abruptio placentae where "too little and too late" is an apt description of the treatment employed. It is difficult to estimate the amount of blood required as the external bleeding is no indication of the volume of the total blood loss. A further difficulty is that shock may result from relatively slight concealed hemorrhage.

The clinical management in this series presented a wide range of treatment. It has been shown by experience that if the patient can be tided over the period of acute renal failure until regeneration of the damaged kidney cells occurs, the patient will survive.[17] Strauss[13] has emphasized that overtreatment with excess fluids has caused death in those who might otherwise recover. Our experience in this respect confirms his opinion. Earlier in this report it has been shown that one cannot estimate the severity of the renal lesion from the urinary findings or blood chemistry, at least in the initial stages. We have been unable to confirm Gibberd's[14] views that frank blood in the urine is diagnostic of cortical necrosis. Gross blood was present in 2 of our fatal cases and in neither was cortical necrosis found at postmortem. On the other hand, gross blood was absent in the single instance where cortical necrosis was demonstrated at autopsy. Due to the complications associated with many of these cases and the therapy employed, it was impossible to ascertain the relationship of fever on the second, third, or fourth day of oliguria as a diagnostic sign of cortical necrosis as suggested by MacGillivray.[11] Pituitrin as an exciting or contributing cause of renal shutdown was not present in any instance. That it could be of significance as suggested by Hertig[15] cannot be disputed. It is questionable, however, whether its use prior to development of shock would be more or less detrimental than withholding it.

As to treatment of the renal lesion, the great majority of cases have responded satisfactorily to a regime of balanced fluid intake with protein-spar-

ing constituents as suggested by Strauss and Bull and associates.[18] In those patients in whom this has failed or seems about to fail, the use of some form of dialysis, intestinal or peritoneal, or artificial kidney is justified. Personal experience with the two former methods has been limited and to a degree successful.

The value of these methods is difficult to determine. There is no question that waste nitrogenous material can be removed in considerable quantity. Their use should be limited to those patients who fail to respond to more conservative measures. The great care required to maintain chemical equilibrium is illustrated in the cases in which they were employed. The intestinal method is simpler and quite as effectual without some of the dangers inherent in peritoneal dialysis.

Dr. Gordon Murray[16] of Toronto has had extensive experience with the artificial kidney where other methods have failed and reports some 50 per cent success. All methods of dialysis require great attention to the alterations in blood chemistry and, with the artificial kidney, a degree of surgical skill which may not be available at all times. In this series, it was utilized on two occasions by Dr. Murray with survival in one instance. The value of transplantation of kidneys in such cases remains uncertain. The availability of such therapy and the skill to utilize it are limiting factors in its general application.

The use of decapsulation and sympathetic nerve blocks has not been productive of improvement. It is our opinion that the former may be sufficient to cause a fatal outcome where the outlook is already hazardous. The latter have not influenced the course of any patients upon whom the treatment was applied.

Conclusions

1. A series of 23 obstetrical and gynecological cases complicated by acute renal failure is presented.

2. The management should be one of conservative maintenance of a balanced intake of fluid and protein-sparing glucose and fat.

3. The utilization of one of the various techniques of dialysis in those patients who fail to respond to this regime is indicated in a small percentage of cases.

4. The development of a more compact and simplified artificial kidney may be of value as its use becomes more widespread.

We wish to thank Drs. W. G. Cosbie, Gordon Murray, R. A. Kinch, and J. C. McKellar for permission to include their cases in this series and Drs. J. D. Hamilton and W. Anderson for confirmation of the pathological findings included in this report.

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Discussion

DR. A. W. DIDDLE, Knoxville, Tenn.—It will be my intention to limit by discussion to two problems in acute renal failure: one, acute renal failure as a cause of death and, two, blood transfusion as a causative agent.

Dr. Cannell has found as others have that in spite of recommendations to limit the administration of fluids during the early phase of acute renal failure, it is not uncommon for patients afflicted with this complication to be given too much fluid. As a result they die from left ventricular failure. Many physicians cannot resist giving excessive fluids in the belief that the kidney will be stimulated to increase its output. Contrary to this view, there is often a delay in water elimination so that water escapes from the blood and accumulates in the extracellular fluid compartments. In response, the diseased kidney may actually proceed to retain water as though responding to generalized dehydration, with the result that the total body water is abnormally increased in amount. The following case history is illustrative.

A few months ago an older colleague of mine acquired acute renal failure with oliguria from a questionable cause. Within a period of several days more than ten consultants saw him. Without exception each recommended or abided by previous advice that the intake of fluids be increased. None suggested they be limited to the estimated daily loss. Gradually the patient acquired generalized edema. Finally, since it was the opinion of those in attendance that he would not survive, all treatment was considered hopeless and discontinued. Thereupon he partially recovered and is still living.

The same tendency to crowd the intake of fluids not uncommonly prevails in the treatment of eclampsia. There is no quarrel with those who prefer the hydration over the dehydration treatment for this kind of patient, provided the impediment of renal work is given intelligent consideration. Failure to make this differentiation was, at least partially, the cause of death in two and the waterlogging of a third out of a total of four eclamptic patients treated in one hospital in Knoxville during the summer of 1951. It is my observation that many gravid patients with renal insufficiency succumb from too much rather than too little treatment with fluids.

The second part of my discussion concerns blood transfusion reactions in the cause of lower nephron nephrosis. DeGowin is of the opinion that probably one to five hemolytic reactions per thousand transfusions will inevitably occur because of human error (DeGowin, E. L., Hardin, R. C., and Alsever, J. B.: Philadelphia, 1949, W. B. Saunders Company, p. 280). Lucké, studying 538 fatalities from acute renal insufficiency, found that blood transfusion was commonly implicated as a probable causative factor (Ducké, B.: Mil. Surg. **99**: 371, 1946). Thus it is apparent that blood transfusion in average hands may carry a formidable potential hazard and makes the procedure one not to be undertaken lightly. In Knoxville, there are an estimated ten thousand transfusions given annually. Accurate figures on the incidence of hemolytic transfusion complications are unavailable but it is known the incidence ranges from insignificant to not infrequent in the various Knoxville hospitals. In contrast, Dr. Cannell had only one instance of acute renal failure attributed to mismatched blood over a ten-year interval in an extensive experience. Assuming that blood transfusion is commonly used in the Toronto Hospitals surveyed, this is an enviable record.

A three-year experience ending Aug. 1, 1952, at the East Tennessee Baptist Hospital makes it apparent that hemolytic reactions from blood transfusion can be largely eliminated through a systematic command of the Transfusion Service. The blood bank in the

Baptist Hospital is under the jurisdiction of Dr. J. Roberts, a full-time pathologist. All blood is drawn into a sterile vacuum container, citrated, stored, and dispensed through sterile plastic tubing by trained technicians. Blood is not taken from potential donors with hemoglobin of 13 grams (85 per cent) or less, with history of syphilis, malaria within 15 years, icterus, current or recent infection, immunizations within six weeks, or who have eaten a meal within three hours. Preserved blood older than 21 days or unused blood left outside the icebox more than one hour is destroyed. Blood from donor to patient is double checked from start to finish by separate persons. Containers are disposed of after being used once. A major and minor cross match is done for every transfusion given, inclusive of O blood, for the reason that some universal donors have been found potentially dangerous. In order to keep fresh blood of various types available, two pints for one used is required. Rare types of blood packed in dry ice and shipped by air are often obtained from New York City and Philadelphia. All blood is given cold and promptly after its removal from cold storage. In all suspected transfusion reactions the cross match is rechecked and the patient followed with icteric index and 24 hour urine specimens.

Over 10,000 blood transfusions have been administered in this hospital during the three years. With this system of control, there was only one known instance of a hemolytic reaction due to mismatched blood in a conscious woman. Fortunately, the error was discovered soon enough after transfusion was begun to prevent harm to the patient. On the other hand, it is impossible to make a dogmatic statement concerning hemolytic reactions and renal failure in unconscious patients. Dr. Forest Powell, now reviewing all postoperative deaths in the Baptist Hospital, found an occasional example of acute renal failure that appeared immediately postoperatively in patients transfused while anesthetized. There were always other complications that occurred simultaneously and that could have accounted for the renal disease. Nevertheless, it was impossible for him to deny that administered blood might possibly have been implicated, partially at least, in an occasional fatality from renal insufficiency. This suggests the potential hazard of giving blood to the unconscious as compared to the conscious patient. It also raises a question in my mind as to whether or not hemolytic complications were implicated in any way in the production of acute renal failure among Dr. Cannell's patients transfused while in shock, exclusive of the one example he described.

DR. JOSEPH W. O'CONNOR, Worcester, Mass.—That the many and complex factors involved in the causation of acute renal failure are a challenge to one's powers of interpretation is evidenced by the vastness of the literature pertinent to this syndrome. The recent articles by Lucké, Strauss, and Chesley cite a total of more than 200 references, the majority of these published in the past decade. There is, however, a lack of articles on the subject from the field of obstetrics and gynecology in which one would expect a fairly large number of cases from the toxemic group on the one hand and the hemorrhage-shock group on the other.

It seems inevitable that abruptio placentae should have furnished the highest incidence of renal failure in this series of Dr. Cannell, in that of Chesley and Young, and in an unpublished series of this discusser, for the syndrome of abruptio embraces nearly all the important etiological as well as the precipitating factors essential to the production of the lesion, from pre-existent toxemia to fulminating separation of the placenta.

Because of the very ominous role played in renal failure by abruptio placentae, I have elected to limit my comments to that phase of Dr. Cannell's paper. That hemorrhage and shock in abruptio placentae are frequently followed by reduced renal function is very well recognized. It has also been my observation, based on a review of 78 cases of abruptio placentae seen since 1920, that shock progresses more rapidly and is more profound when the hemorrhage is concealed rather than patent, and, by the same token, that the threat of renal failure seems to occur earlier and is more severe. Similar observations have been made by Young and Chesley, but those of Dr. Cannell, on the other hand, do not support this contention. While the mechanism of acute renal failure is still incompletely solved, Mallory's theory that glomerular filtration is seriously reduced in

shock has found many supporters. While this phenomenon may account for the initial oliguria of renal failure it does not entirely explain its persistence.

The theory of damage to the tubules, probably by toxins, seems to provide a fairly logical explanation of the continuance of lowered urinary output. The research of Mallory, Lucké, Strauss, and others has established that damage in the form of cell necrosis and tubal rupture in the lower nephron is a constant finding and that these lesions, along with mechanical obstruction of the tubules by casts composed of precipitated heme pigments, may be the determining factor in the reduction of urinary output. Lucké, in his microphotographs of lower nephron lesions, has demonstrated the presence of this type of cast especially in the distal convoluted and collecting tubules.

The origin of the heme compounds forming these casts is attributed by Baker and Dodds to the breaking down of the hemoglobin molecule resulting in precipitations of hematin in the intratubular fluid when its acidity falls below pH 6.0 and its sodium chloride content reaches 1 per cent. The fact that these requirements are met in the lower nephron and collecting tubules seems to account adequately for the almost constant presence of heme casts in the lower renal segments.

In cases of renal failure in crush wounds myohemoglobin tends to play a rather important part and the muscle destruction which brings it about is suspected of contributing largely to the phenomenon of tubule obstruction. In the light of this observation one is prompted to venture the perhaps fantastic theory that the damaged uterine muscle and the extravasation of blood at the site of the abruption may contribute hemoglobin and perhaps myohemoglobin for the formation of the heme casts which are believed to account, at least in part, for the temporary failure of urinary output.

I am in complete accord with Dr. Cannell and Dr. Biddle that there are certain things which we have been overdoing and certain things which we probably are not doing well enough. To Dr. Cannell's thorough discussion of treatment there is little for me to add. It may not be amiss, however, to emphasize the importance of employing the following standard measures: (1) Blood transfusions for the initial shock and hemorrhage, but thereafter, in general, rather a little less than a little more. (2) Fluid in frequent, small infusions to maintain the proper water balance, but avoid overdoing it because edema of the lungs is one of the most frequent immediate causes of death in this disease. Finally, (3) the use of dextrose up to 100 Gm. daily may not only prevent damage to the liver but help to support life in the patient until such time as spontaneous recovery from the lesion may take place.

DR. FRANK LOCK, Winston-Salem, N. C.—The survey of maternal deaths which has been conducted over the past ten years by the Maternal Welfare Committee of the North Carolina State Medical Society has shown that oliguria and anuria are the primary causes of death in 1 out of 10 fatal cases of toxemia of pregnancy.

It is fortunate that the treatment of urinary suppression is becoming stabilized and that it has become more and more conservative during the past ten years.

We have published slides which summarize the treatment, chemical findings, and clinical course of 2 patients with severe forms of lower nephron nephrosis who survived (AM. J. OBST. & GYNEC. 60: 820, 1950). I also have a slide showing the record of a patient with true bilateral renal cortical necrosis who died, but remained free of edema and was rational during a twenty-one day period of anuria before her death. Autopsy studies on this patient showed no evidence of regeneration in the kidneys. This case will be reported in detail in the near future.

In each of these 3 cases the patient came under our care after urinary "shutdown" had occurred. Three pints of incompatible blood were given to the first patient while she was being treated for bleeding related to a late abortion; the second patient had abruptio placentae, postoperative hemorrhage, and shock. In the case of bilateral cortical necrosis, the cause was undetermined.

A strictly conservative plan of management was instituted in each case. Anemia was corrected by the administration of carefully matched blood. Fluid was given in a

quantity which replaced that lost through urinary output and insensible means. A moderate fluid deficit is far more desirable than any excess.

Because of its ketolytic action and possible protein-sparing effect in the quantities given, glucose in water is the basis of parenteral treatment. One hundred Gm. of glucose can be given in 500 ml. of water as a 20 per cent solution.

The level of the nonprotein nitrogen is of no prognostic significance and, moreover, of no value from the standpoint of management. However, serial determinations of the carbon dioxide combining power, and serum chlorides, and estimates of total base or sodium are extremely valuable as indicating the necessity for electrolyte therapy. It should be emphasized, however, that the administration of electrolytes is not without hazard. Although correction of acidosis, hypochloremia, and of total base is of great importance, when laboratory determinations are uncertain or equivocal it is better to err on the conservative side.

The danger of undertreatment in the period of diuresis is as great as that of overtreatment in the acute phase of anuria. Loss of salt and fluid may be tremendous, and they require prompt replacement. It is noteworthy that one of our patients lost 23.3 Gm. of sodium chloride and more than 5 L. of fluid in one 24 hour period of diuresis.

Transperitoneal lavage and the use of the artificial kidney are heroic measures. Their usefulness has been demonstrated in a few centers. However, we believe that these measures are rarely indicated and agree with Dr. Cannell that they should be reserved for those rare patients who are rapidly losing ground under a conservative regimen.

DR. E. STEWART TAYLOR, Denver, Colo.—I would like to emphasize the differential diagnosis between lower nephron nephrosis and the syndrome that we discussed, namely, adrenal cortical insufficiency.

Lower nephron nephrosis has been well covered by Dr. Cannell. There usually is a specific episode of trauma, toxicity, shock, transfusion reaction, or drug reaction that antedates lower nephron nephrosis. The patient recovers from the specific episode of shock, trauma, or toxicity but is found to have anuria as a prominent residual sign. The treatment then, as outlined by essayist and the discussers, is extremely important, mainly as it entails the proper withholding of fluids instead of the administration of fluids.

Let me contrast this to the syndrome of cortical adrenal failure which is important because in our own experience we have encountered difficulty in the differential diagnosis between these two conditions. In the adrenal cortical syndrome the patient is in apparent good health before her operation and suffers no particular shocking or toxic episode at surgery. She is operated on and then in a period varying from one to five days after the operation an episode of vasomotor collapse occurs. At this time a diminished urinary output or anuria may be part of the clinical picture. It may be a temptation because of the anuria or oliguria to make a diagnosis of lower nephron nephrosis. The episode of delayed shock accompanied by urinary suppression is not lower nephron nephrosis, it is more likely to be cortical adrenal insufficiency. It is an important differential diagnosis because the treatment here is the exact opposite from the one that has been described by Dr. Cannell for lower nephron nephrosis. With cortical adrenal insufficiency there must be replacement of sodium chloride, water, and the all-important cortical substances in an energetic manner.

Whenever a death has occurred due to the lower nephron nephrosis, or the "hepatorenal syndrome," it has been my experience, on looking into the literature, that the adrenal glands, because of their peculiar anatomical position, have not been very interesting to the pathologist or at least have not been until recently, and so he has not dissected them from the surrounding fat and subjected the organ to careful gross and microscopic examination. The same holds true for the pituitary gland. For various reasons it is often not examined, or is not fixed properly, and does not enter into the complete story when the autopsy protocol and conclusions are finally summarized.

DR. F. H. FALLS, Chicago, Ill.—It is important that the hypophysis be carefully studied in all patients who die under the conditions described in this paper. This is not

always easy to do because many of these patients are not autopsied and in many of those who are autopsied the head is not included. It is the duty of the clinician to insist on an examination of the brain with particular reference to the hypophysis.

I wish also to call attention to the danger of blood transfusion in these patients. It is obvious to me, from personal observation and from reading the protocols prepared for the Illinois State Medical Society Maternal Welfare Committee, that many of the cases were best explained on the assumption that the blood given reacted abnormally after injection even though it was properly typed and matched according to our standard methods. I believe that the ordinary laws for blood transfusion do not always apply when the patients are suffering from toxemia of pregnancy or premature detachment of the placenta.

DR. CANNELL (Closing).—Acute renal failure is not particularly important from the standpoint of numbers. Our 23 cases occurred in approximately 50,000 admissions to the hospital, yet the disease does represent a substantial fraction of the total number of maternal deaths. Anything that can be done to improve the situation, therefore, is significant.

In regard to blood transfusion and the incidence of reaction, I pointed out that probably more than one factor was operative in these cases. The single reaction that occurred in this particular clinical group does not of course represent all the transfusion reactions during these years.

GLUCOSE TOLERANCE AND EXCESSIVELY LARGE BABIES IN NONDIABETIC MOTHERS*

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EXCESSIVELY large babies, parental pride notwithstanding, are unwelcome obstetric hazards. For years the association of excessive fetal size with maternal diabetes mellitus has been axiomatic although no more than 20 to 25 per cent of these diabetic mothers deliver such infants. More recently this relationship has been extended to the prediabetic state.[1-5] Some observers[6, 7] report that many if not most of the nondiabetic mothers who have excessively large infants ultimately become diabetic. Obstetricians customarily have linked the big baby with postmaturity, maternal weight gain, obesity, age, multiparity, heredity, and no doubt many other factors. Newer studies[8, 9, 29] have disproved, bit by bit, these ideas of postmaturity and excessive weight gain. Others suggest that parity and age are incidental rather than etiological factors.

Sporadic interest in glucose tolerance, renal glycosuria, alimentary hyperglycemia, and related aspects of carbohydrate metabolism has existed for the past thirty years. Early interest was centered chiefly on the diagnosis of pregnancy by the demonstration of a lowered renal threshold to glucose. In recent years the interest has been directed toward the significance of glycosuria and its relation to the diagnosis of diabetes.[10-13]

It is our purpose to review and to extend the studies of glucose tolerance in normal pregnancy, to correlate abnormal glucose tolerance with babies of excessive size, to present preliminary work on the cause of abnormal tolerance, and, finally, to discuss some of the important obstetrical aspects of fetal gigantism.

Methods and Materials

This study of all women delivered of excessively large infants by the Louisiana State University Unit of Charity Hospital began in 1949 as a pilot clinical-laboratory project. From March, 1951, to July, 1952, a detailed study was continued in the departmental research laboratories. Excessive fetal size has been customarily set at 4,500 grams and we have followed this arbitrary custom.

A total of 170 glucose tolerance tests were done on 138 patients, including 68 made upon 51 women having excessively large infants. The remainder were control studies, cortisone studies, and studies of complicated pregnancies.

Every effort was made to have the patient in good carbohydrate balance before testing. Tests were done routinely at 9 A.M. following overnight fasting. Tests were not done during the first 48 hours post partum because of the

*Presented at the Sixty-third Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, Hot Springs, Va., Sept. 4 to 6, 1952.

alimentary disturbances common to labor and delivery. All laboratory determinations were done by one specially trained technologist.

Technique.—An indwelling catheter was placed in the bladder and the bladder was emptied. A sample of venous blood was drawn, following which the patient took orally 100 Gm. of glucose dissolved in 300 c.c. of water flavored with lemon juice. Specimens of blood and urine were obtained one-half, one, two, and three hours thereafter. Blood sugar was determined by the method of Folin.[14] Urine sugar was determined quantitatively by the method of Folin and Svedberg[15] upon the total volume during each period of time. Accordingly urine sugar was reported in milligrams per cent and in total excretion per time interval.

Quantitative fermentation[16] studies were done routinely upon each fasting blood sample after preliminary testing had revealed that nonfermentable substances remained essentially unchanged during the course of a glucose tolerance test. The type of yeast used is important. The average amount of nonfermentable substances remaining after use of Red Star yeast was 18 mg. per cent, while after Fleischmann's yeast it was 7 mg. per cent and, consequently, the latter was used. A comparison of the two yeasts is shown in Table I.

TABLE I. DUPLICATE AND TRIPLICATE SAMPLES SHOW THE EFFECTIVENESS OF FLEISCHMANN'S YEAST OVER RED STAR YEAST IN BLOOD FERMENTATION

	NONFERMENTABLE SUBSTANCES (MILLIGRAMS PER CENT)	
BLOOD SAMPLE	FLEISCHMANN'S	RED STAR
No. 1	5	16
	6	17
No. 2	6	21
	8	21
No. 3	5	20
	5	20
No. 4	8	15
	8	16
	8	16
No. 5	7	16
	7	16
	7	17

Renal Threshold and Glycosuria

To the best of our knowledge the renal threshold for glucose during pregnancy has not been accurately determined although most of us have glibly said that the threshold is lowered. The accurate measurement of renal threshold is a difficult task which, incidentally, we have not accomplished. We have, however, measured quantitatively the concentration and total amount of urinary reducing substances under fasting conditions and during testing of glucose tolerance. The concentration of urinary sugar usually varies inversely as the volume, excluding renal threshold for the moment. For this reason we have insisted upon an hourly urinary volume of at least 100 c.c. We then calculated the sugar excreted hourly during the three-hour period of the test. The total output in milligrams divided by three was our unit of measure.

Under fasting conditions only small amounts of reduction were noted (Fig. 1, *A*). Thirteen of 124 patients (10 per cent) had concentrations above 100 mg. per cent but none reached 200 mg. per cent, which is no more than a trace in terms of Benedict's qualitative test. Nine of these 13 patients had a lowered renal threshold.

In 70 patients the maximum elevation of blood sugar during tolerance testing failed to reach threshold levels. The generally accepted renal threshold for sugar is 175 ± 5 mg. per cent. Twenty-one of the 70 patients (30 per cent)

spilled over 300 mg. of urinary sugar during the test, an average of 100 mg. or more per hour (Fig. 1, *B*).

Quite unexpected was the evidence that some pregnant women developed an elevation of renal threshold. Patients who spilled less than 300 mg. of glucose during the test in the presence of blood sugar exceeding 180 mg. per cent were considered to have an elevated threshold. Fig. 1, *B* also shows that 6 of 32 (20 per cent) patients with maximum blood sugar levels above 180 mg. per cent had elevated renal thresholds.

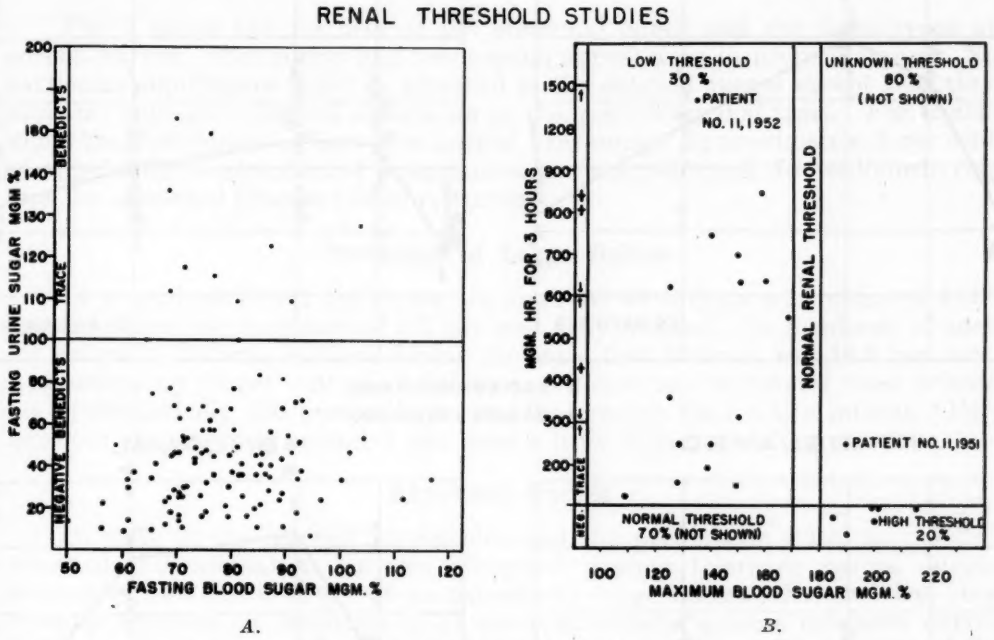


Fig. 1.—*A*, A scattergraph plotting the fasting blood sugar against fasting urinary sugar. *B*, Illustrates the depression as well as the elevation of the renal threshold in normal pregnancy.

Fermentation Studies

Fermentation studies by Richardson and Bitter[17] demonstrated that nearly half of the urinary reducing substances during pregnancy were other than glucose and that during the puerperium the nonfermentable substances were even higher. Fermentation studies upon the blood have not been reported. For this reason and to insure accuracy of data 90 fermentation tests were done. Mean values were 8.3 mg. per cent with a range of 4 to 14 mg. per cent. There was no significant variation during any trimester of pregnancy, early or late puerperium, whether or not lactation was present. Nonpregnant controls had a mean of 8.9 mg. per cent with a range of 5 to 13 mg. per cent.

Types of Curves

The most important and most difficult task was classification of the curves. What is normal or abnormal during pregnancy? Little is known about glucose tolerance in normal pregnancy. Many of the studies have been done upon women with glycosuria or some disorder of carbohydrate metabolism. However, Williams,[18] Richardson,[17] Hurwitz and Jensen,[19] Weiden,[10] and Basil-Jones[11] agree generally that during pregnancy the glucose tolerance curve is no higher than normal, except at the two- and three-hour reading. Often the curve may be a little lower than normal at fasting, at one-half hour, and at one hour.

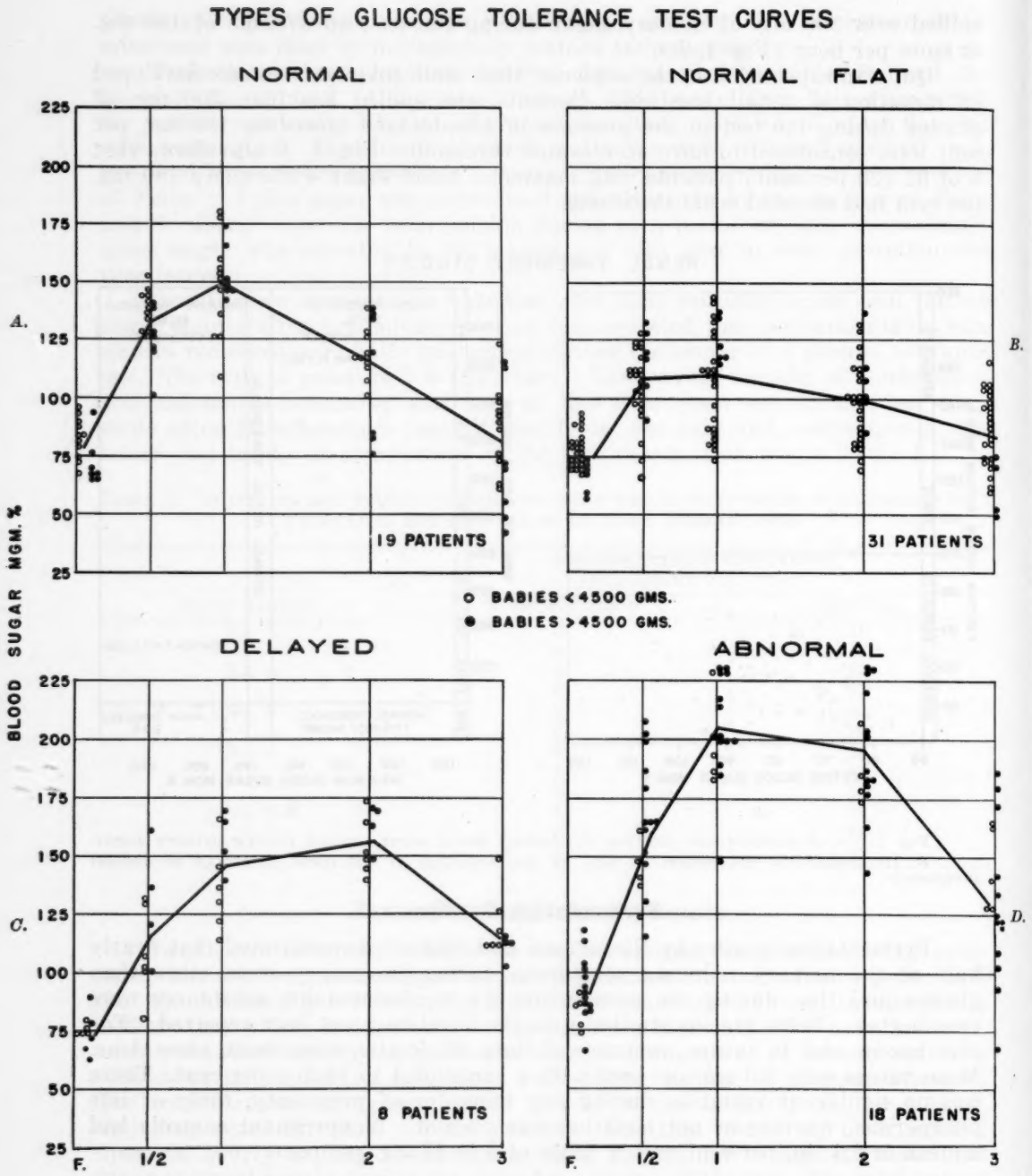


Fig. 2.—*A*, The typically normal glucose tolerance curve. The heavy line is the mean.
B, The flat curve which is the most common type during normal pregnancy.
C, The high two- and three-hour levels of the delayed curve.
D, Abnormal curves are usually indistinguishable from diabetic curves but are not necessarily diabetic.

There is justifiable disagreement on the classification of abnormal curves and their clinical significance. For reasons to be mentioned later, we hesitate to label an abnormal curve in pregnancy as diabetic without other confirming clinical or laboratory data. Our classification has been made after graphic

plotting of each curve and sorting into obviously similiar categories. It is surprising how readily most of the curves fall into normal and abnormal groups.

Abnormal curves are characterized by the following blood sugar values:

Fasting: Usually above 80 mg. per cent (Fig. 2, *D*).

One-half and/or *one hour:* Above 180 mg. per cent.

Two hours: If it is the peak, above 175 mg. per cent, or if the peak occurred earlier, above 160 mg. per cent.

Three hours: Generally above 125 mg. per cent, unless the peak occurred early.

Fig. 2 shows the features of the abnormal curve and the three types of normal curves. Flat curves and low normal curves were in preponderance. No particular significance could be attached to the delayed curves except that they probably represent delayed absorption in the gastrointestinal tract. Fig. 2 also shows the distribution of curves in normal pregnancy. Approximately 8 per cent of apparently uncomplicated pregnancies are characterized, for unknown reasons, by abnormal glucose tolerance curves.

Incidence of Large Babies

In a total of 13,502 deliveries, we observed 61 infants who weighed 4,500 grams or more, an incidence of 0.5 per cent. By contrast, the incidence of such big babies in diabetic mothers during the same time interval was 14.5 per cent. Approximately 80 per cent of all babies were Negro and in general these infants are approximately 250 grams lighter on the average than white infants. Perhaps our standards of excessive size were a little high in the Negro group.

Abnormal Curves

In spite of the interest in diabetes and the prediabetic state, no one has reported the correlation between abnormal glucose tolerance curves during pregnancy and the delivery of an excessively large infant. Kritzer[7] has very recently reported an incidence of 31 per cent diabetic glucose tolerance curves in nonpregnant women who had previously had large babies. We have carefully studied 30 mothers delivered of excessively large babies, 6 delivered of intermediate-sized babies, and 58 normal controls. Table II shows the incidence of the various types of curves. Less than 10 per cent of normal women having normal-sized babies showed abnormal tolerance, but 44 per cent of the mothers (diabetics excluded) of the large babies had abnormal glucose tolerance. No attempt was made to study the intermediate weight group but preliminary data indicated a similarity to the excessive-sized group so far as maternal glucose tolerance was concerned.

Many combinations and permutations are possible in dealing with the problem of big babies, abnormal curves, and other factors. Table III shows that about half of the women who delivered excessively large infants had done so

TABLE II. THE WEIGHT OF THE NEWBORN INFANT IS DEFINITELY RELATED TO AN ABNORMAL MATERNAL GLUCOSE TOLERANCE ($x^2 = 14.4$)

WEIGHT OF BABY (GRAMS)	MATERNAL GLUCOSE TOLERANCE		
	ABNORMAL	NORMAL	TOTAL
<3,800 Normal	5	55	60
3,800-4,500 Intermediate	3	3	6
>4,500 Excessive	13	17	30
Total	21	75	96

previously. However, when these are further subdivided according to glucose tolerance we see that abnormal curves are limited primarily to the women having the second or third big baby.

TABLE III. MOTHERS WITH A PREVIOUS HISTORY OF EXCESSIVELY LARGE INFANTS ARE VERY LIKELY TO HAVE ABNORMAL GLUCOSE TOLERANCE IF THEY DELIVER A BIG BABY IN A SUBSEQUENT PREGNANCY ($x^2 = 10.8$)

PREVIOUS HISTORY OF BIG BABIES	ABNORMAL CURVE	NORMAL CURVE	TOTAL
One or more	12	4	16
None	1	12	13
Total	13	16	29

Also recorded was the incidence of abnormal curves in nonpregnant women who had a history of fetal gigantism, similar to the study of Kritzer.[7] There were 20 women in this category; 5, or 25 per cent, had abnormal curves, including two with unsuspected diabetes.

Postpartal Changes

One of the unusual and unexpected features was the change in tolerance which followed delivery (Table IV). Twelve of the mothers who had abnormal curves late in pregnancy or at delivery were again studied 4 to 10 months later. At this time only 5 had abnormal curves. One patient with abnormal curves and excessively large babies during two successive pregnancies promptly returned to normal each time after delivery. Fig. 3, *A* shows the average values for these 12 patients on the second to the fifth day post partum and four to ten months later. When these data were discovered it was necessary to see if a significant drop in the tolerance curve might occur as early as the second postpartal day. This proved to be the case. Four patients suspected of carrying excessively large infants were shown to have abnormal curves during the last month of pregnancy. Within three days after delivery of big babies all but one had normal tolerance and later this one also returned to normal (Fig. 3, *B*). We

TABLE IV. POSTPARTAL CHANGES OF ABNORMAL GLUCOSE TOLERANCE CURVES. SAMPLES IN MILLIGRAMS PER CENT AT FASTING, ONE-HALF, ONE, TWO, AND THREE HOURS

PATIENT	LATE PREGNANCY OR EARLY POSTPARTUM PERIOD	4 TO 10 MONTHS POST PARTUM
Curves Returning to Normal.—		
28	88-206-245-163- 66	77-128-135-124-101
30	82-147-199-181-123	64-121-143-119- 84
37	102-164-215-175-121	89-136-169-136- 81
49 (1951)	113-199-239-219-171	84-104-118- 98- 94
49 (1950)	100-170-220-175-125	70-104-125-125-100
71	83-169-189-181-100	87-132-151-121- 87
65	84-147-241-233-163	78- 85-121- 85- 85
107	112-200-233-222-128	103-159-162-144-100
Curves Improved.—		
25	75-163-201-197- 58	88-126-192-166- 50
77	74-147-178-200- 91	73-184-176-118- 82
85	93-164-199-184- 92	106-179-164-111- 68
Curves Worse.—		
89*	92-164-229-246-136	159-203-285-306-285
OS35*	75-160-180-160-155	110-135-160-180-175
E. L.†	99-178-249-268-278	173-261-333-285-250
E. S.†	121-236-284-296-248	248-324-392-408-365

*Discovered diabetic patient.
†Known diabetic patient.

have no way of knowing how many abnormal curves we missed by waiting 48 hours after delivery before testing glucose tolerance but at least 3 would have been missed had we not done tolerance tests prior to delivery.

Ten patients with normal curves have been studied post partum. There is a similar tendency for the high normal curves to fall but obviously not so in those with flat curves.

Not all patients demonstrated this postpartal lowering of the curve. It has been established that the glucose tolerance curves in the diabetic patient may fall during pregnancy and rise again after delivery. We have observed such changes in 4 patients, 2 of whom were known diabetics, 2 were discovered as mildly diabetic by this study (Table IV).

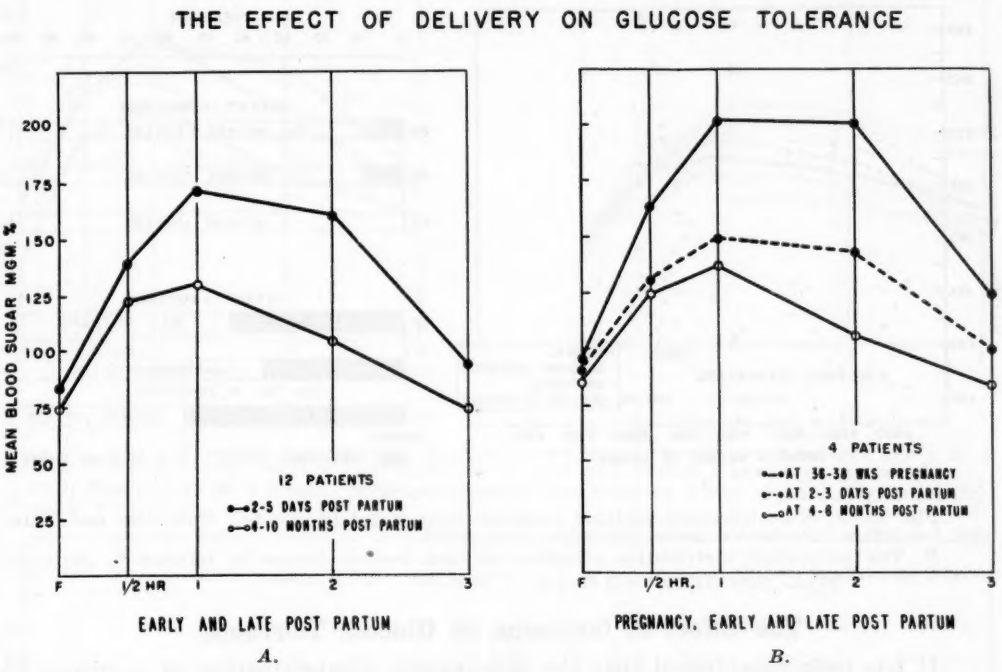


Fig. 3.—*A*, The mean of 12 abnormal curves studied shortly after delivery and again several months later at which time all were normal.

B, The rapid fall of the glucose tolerance curve which may occur within two days after delivery and the further fall to normal during the puerperium.

Obesity and Abnormal Curves

Maternal weight gain has no great bearing on excessive fetal size,[9] but this cannot be said of obesity. In this study we have called obese the woman whose maximum weight during pregnancy exceeded 200 pounds. The incidence of obesity was approximately 10 per cent. Half of all the big babies have obese mothers. It immediately follows that the incidence of excessive fetal size in obese mothers is 10 times greater than in the nonobese mother, or 2.5 per cent and 0.25 per cent, respectively.

TABLE V. SHOWS THAT LARGE BABIES ARE MORE COMMON IN OBESE WOMEN WITH ABNORMAL CURVES THAN IN OBESE WOMEN WITH NORMAL CURVES ($x^2 = 5.5$)

OBESE MOTHER WITH	WEIGHT OF INFANTS (GRAMS)		TOTAL
	>4,500	<3,800	
Normal curve	0	12	12
Abnormal curve	7	6	13
Total	7	18	25

Fig. 4 shows the incidence of abnormal curves in obese and lean mothers who were delivered of normal as well as of excessively large infants. Although we obtained tolerance tests on all obese women who had big babies we did not study all obese women. This would be essential if the relation of obesity to abnormal curve is to be absolutely established. Table V is a breakdown of part of Fig. 4, *B* and shows that every obese woman with an abnormal curve had a big baby; however, many obese women (45 per cent) with normal curves also had big babies. It would appear that either maternal obesity or abnormal glucose tolerance will influence fetal size but a combination of the two is indeed a potent etiological force.

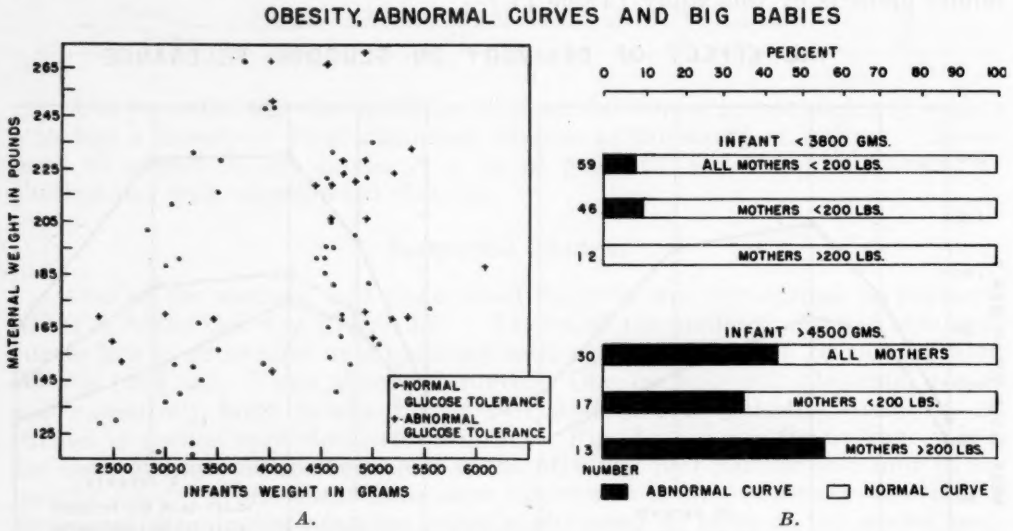


Fig. 4.—*A*, A scattergraph plotting maternal against infant weight. This does not represent frequency distribution below the 4,500 gram level.

B, The percentage distribution of abnormal and normal curves in relation to maternal weight and infant weight.

The Effect of Cortisone on Glucose Tolerance

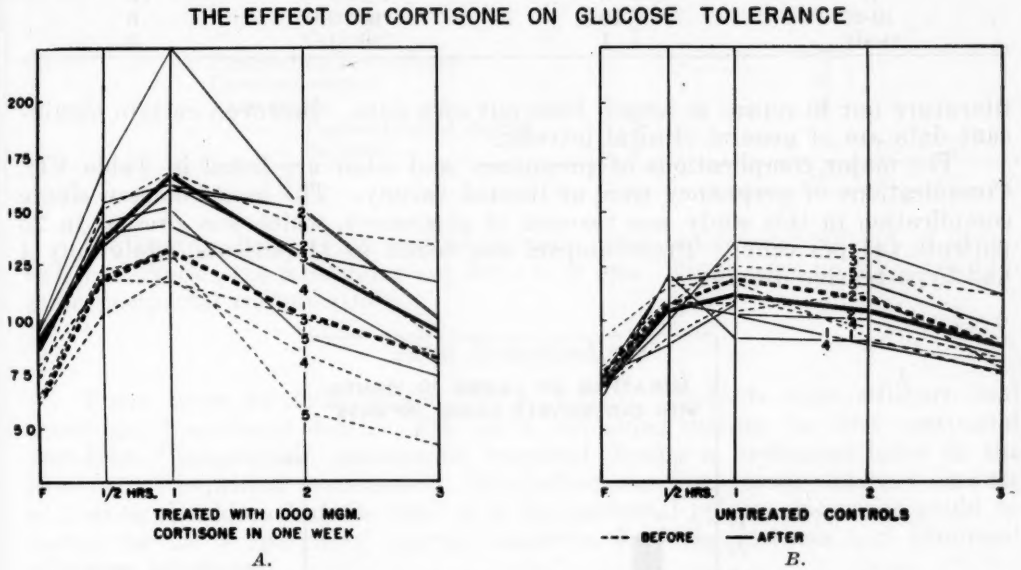
It has been established that the therapeutic administration of cortisone to nonpregnant individuals will produce glucose intolerance.[20] Administration of the drug to normal male subjects will also produce elevation of the glucose tolerance curve.[21] Carefully controlled preliminary studies in our laboratory indicate that a similiar change will occur during pregnancy. Ten normally pregnant women without personal or family history of diabetes were studied under identical conditions of diet, care, and activity. Five received 1,000 mg. of cortisone* intramuscularly during a seven-day period in the following dosage: first day, 300 mg., second day, 200 mg., and then 100 mg. daily for five days. The control patients received intramuscular injections of an equal volume of normal saline. Glucose tolerance was determined before therapy and on the morning following therapy. Fig. 5 shows increase in blood sugar values of 24 of the 25 samples of treated patients. The average increase varied from 16 per cent in the three-hour sample to 33 per cent in the fasting sample. By contrast the control group remained essentially unchanged, although demonstrating minor individual variations.

Other Etiology

Studies of this type in the past have made much of age, parity, maternal weight gain, and heredity. In reviewing our data we could find no correlation

*Cortisone for this study was furnished through the courtesy of Merck and Company.

with weight gain. It was interesting to compare parity and age (Table VI). There is no doubt that increasing parity and increasing age are associated with big babies but it would be unusual if not impossible to have great multiparity in a young person. However, it is significant that not a single large baby was delivered from mothers less than 20 years old although we have many patients in that age bracket.



A. *B.*

Fig. 5.—*A*, The universal increase in every specimen of the glucose tolerance curve in 5 normal pregnant women treated with 1,000 mg. of cortisone during a period of one week.

B, The results in 5 normal pregnant controls who received 5 c.c. of normal saline daily. There is no change.

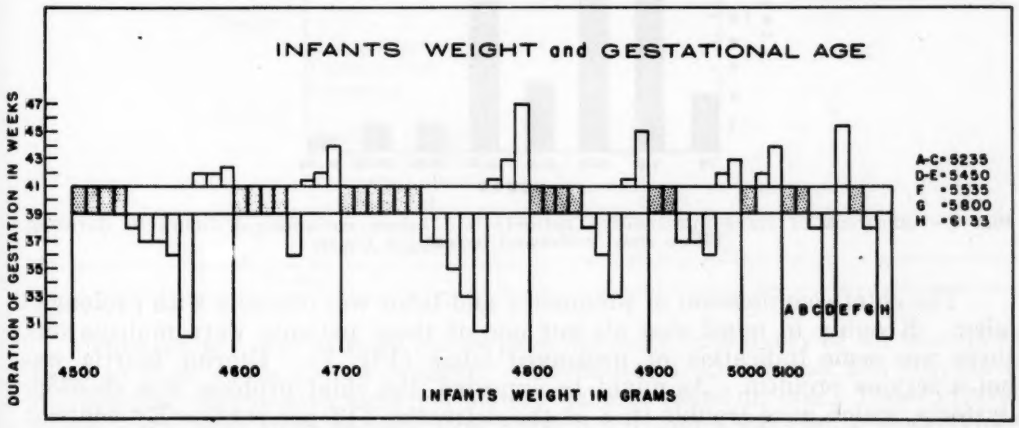


Fig. 6.—Only 16 of 61 mothers had postmature infants according to menstrual history and of these only 6 were beyond 42 weeks' gestation, while 24 mothers were delivered at the expected date and 21 were delivered from 2 to 10 weeks "prematurely."

One cannot discuss this problem without introducing the question of postmaturity. Fig. 6 shows that there were relatively few babies with a clear-cut history of postmaturity, more were "premature" by history. Neither can be accepted as accurate.

Complications of Pregnancy and Labor

Several papers,[22-29] mostly foreign, have described the clinical features of fetal gigantism. As these are so well known we make no attempt to review the

TABLE VI. BIG BABIES ARE FOUND IN WOMEN WITH INCREASING PARITY AS WELL AS AGE.

PARITY	AGE (YEARS)		
	20-29	30-39	40 AND OVER
Primipara	1	0	0
i	2	0	0
ii	5	2	0
iii-v	16	14	0
vi-xiv	1	16	3

literature nor to repeat at length from our own data. However, certain significant data are of general clinical interest.

The major complications of pregnancy and labor are listed in Table VII. Complications of pregnancy were of limited variety. The most common single complication in this study was toxemia of pregnancy, which was present in 25 patients (41 per cent). Pre-eclampsia was found in 21 patients, while only 4 had hypertensive disease.

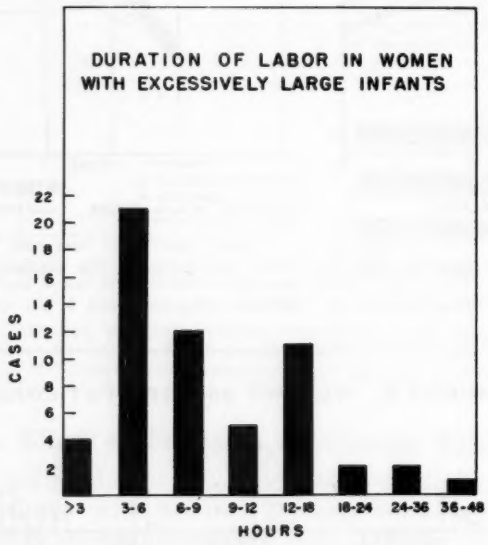


Fig. 7.—One-third of these multiparous patients had labors exceeding 9 hours in duration. Three were prolonged beyond 24 hours.

The chief complication of pregnancy and labor was dystocia with prolonged labor. Keeping in mind that all but one of these patients were multiparous, there was some indication of prolonged labor (Fig. 7). Uterine inertia was not a serious problem. As might be expected, the chief problem was shoulder dystocia, which gave trouble in 8 of the deliveries (13 per cent). By contrast cephalic dystocia occurred once. Vertex presentation was found in 60 of the 61 patients. A single infant in breech presentation was delivered with some shoulder dystocia. There were no face presentations, which is in contrast to Hagblom's[24] observations.

Normal spontaneous delivery was the rule. Two patients were delivered by midforceps and two by cesarean section. Indications for the latter were repeat section and uterine inertia in the presence of estimated excessive fetal size.

No significant cervical lacerations were found, although the cervix was routinely inspected in these patients. There were, however, 2 third-degree perineal lacerations.

TABLE VII. MATERNAL COMPLICATIONS IN TWENTY-FIVE PATIENTS. MULTIPLE COMPLICATIONS WERE THE RULE

Toxemia		25
Pre-eclampsia	21	
Hypertension	4	
Dystocia		11
Shoulder	8	
Inertia	2	
Cephalic	1	
Postpartum hemorrhage		3
Cesarean section		2
Lacerations		2
Perineal, third degree	2	
Cervical	0	
Total		43

Postpartum hemorrhage was uncommon. One patient lost 800 c.c. of blood, two lost 500 c.c., the remainder lost 400 c.c. or less. There were no other troublesome postpartal complications.

Fetal Complications

There were six fetal deaths (Table VIII); 5 infants were stillborn and there was 1 neonatal death. The latter happened during the first postpartal day from "congenital" pneumonia incurred during a prolonged labor in the presence of ruptured membranes. One infant was lost during delivery because of "stuck shoulders" at the inlet of a flat maternal pelvis. No cause could be found for the 4 antepartal deaths; however, 3 of the mothers had abnormal tolerance to glucose.

TABLE VIII. FETAL COMPLICATIONS. TWO OF FIFTY-FIVE LIVEBORN INFANTS WERE DAMAGED PERMANENTLY—ONE DIED AND THE OTHER HAD BRACHIAL PLEXUS INJURY

Death		6
Antepartum	4	
Intrapartum	1	
Neonatal	1	
Injury		4
Brachial plexus (two transitory)	3	
Fractured clavicle	1	
Intracranial	0	
Congenital anomaly		1
Hydrocephalus	1	
Total		11

Thirteen per cent of these babies gave difficulty in delivery of the shoulders. Four of these infants were injured. One died and the other 3 had trauma to the brachial plexus with some permanent damage noted in one. These injured babies were large, their weights were 5,200, 5,220, and 5,500 grams, respectively.

The lone congenital anomaly was a noncommunicating hydrocephalus. Follow-up was impossible but the infant was alive at the time of discharge from the hospital.

Comment

Two changes of sugar metabolism, either physiological or pathological, frequently occur during pregnancy. One is an alteration of renal threshold; the other, an alteration of the normal tolerance to glucose. Four possibilities may therefore exist in any given patient: both may be normal, both may be abnormal, or either one may be abnormal.

Half of all normally pregnant women have some disturbance of renal threshold. About 30 per cent of normal pregnant women spill large amounts of sugar in the urine following glucose ingestion in the absence of elevated blood sugar levels. Twenty per cent have an apparent elevation of renal threshold as they fail to spill significant amounts of sugar in the urine although the blood sugar is above the normal threshold range of 170 to 180 mg. per cent. If, however, quantitative determinations of sugar are made on the fasting morning specimen, then only 10 per cent of pregnant patients show concentrations above 100 mg. per cent. Much apprehension can be spared if in clinical practice all tests for urinary sugar are done upon fresh samples under fasting conditions. The majority of women who spill sugar under these conditions have lowered renal threshold, but this lowering of the renal threshold was not related to abnormal or normal glucose tolerance and cannot be used as a guide in the clinical prediction of abnormal tolerance.

Significant and sometimes profound changes take place in the tolerance to carbohydrates during pregnancy. There is, as a rule, a distinct lowering of normal values for fasting blood sugar. If they are below 75 mg. per cent there is little chance that the patient has abnormal tolerance. These patients usually exhibit a rather low glucose tolerance curve. Usually the peak of the curve is reached sometime during the second hour and the third-hour values are often high in terms of normal nonpregnant values. Unless this delay is marked by a clear-cut intolerance (elevated curve) to glucose it is of no practical significance. Johnson and Bonsnes[30] have been able to eliminate this delay with the use of the intravenous tolerance test. We conclude that the normally pregnant woman may have some interference with carbohydrate absorption but having absorbed the sugar she promptly utilizes and stores it. A few, between 5 and 10 per cent, apparently normal women have a distinct intolerance to carbohydrate during pregnancy, manifested by an abnormal glucose tolerance curve often indistinguishable from a diabetic curve. In fact, many mothers have had erroneous diagnoses of diabetes during pregnancy on the strength of an abnormal tolerance curve.

Our data have shown that the majority of these abnormal curves are produced by some unknown factors of pregnancy. The factors, possibly hormonal, cease to operate soon after delivery and the abnormal curve returns to normal.

There is little doubt that we missed several abnormal curves by waiting until the second or third postpartal day before determining glucose tolerance. We now attempt to anticipate excessive fetal size and obtain glucose tolerance curves prior to delivery and again after delivery and in this way demonstrate the rapid drop of the curve. However, in some patients the curve returns incompletely to normal and in others the curve is worse after delivery. The latter group are undoubtedly diabetic, but what of the others? Are they prediabetic? We think so but have no proof. Continued testing for several years will be necessary.

Half of all the excessively large babies come from one-tenth of the mothers —the obese. As a group, the obese have ten times as many big babies as the nonobese. In spite of this, our data also indicate that an abnormal glucose tolerance curve is even more important etiologically. However, a combination of the two is most potent and suggests the possibility of synergism. The triad of excessive fetal size, abnormal glucose tolerance, and maternal obesity is firmly established.

The factor or factors which produce some of the big babies are closely related to the abnormal control of carbohydrate metabolism and may be mediated through the anterior pituitary. In fact, we have observed a better correlation with obesity, abnormal curve, and big baby (55 per cent) than we have with diabetes and big baby (14.5 per cent), although some authors have reported the incidence as great as 25 per cent.

In practice we determine the blood sugar level of all suspects during the last trimester of pregnancy. If this is elevated or if the patient shows evidence of a big baby by abdominal palpation, then a glucose tolerance test is in order. If the curve is abnormal another test should be done three months after delivery. If the curve is still abnormal, incipient or frank diabetes should be suspected.

ACTH and cortisone are diabetogenic[20, 31] and diabetes has been produced in the rat with massive doses of cortisone. Relatively small doses of cortisone (1,000 mg. in seven days) during pregnancy produced a consistent elevation of fasting blood sugar as well as glucose tolerance curves in 5 patients. Similar changes were not observed in a control group of 5 patients. Although these are preliminary observations their significance should be clear. Further studies on the effects of ACTH and cortisone upon glucose metabolism and fetal size in man and the experimental animal are in progress in our laboratory at the present time.

At least two clinical features of this study point out a possible relationship to diabetes and the prediabetic state. The first is that of toxemia. Pre-eclampsia was present in approximately 25 per cent of these mothers. The other is the problem of antepartum fetal death. Four of 61 infants were lost in this fashion. A careful study of the mothers failed to produce any cause for the death except the so-called "diabetic postmaturity," but it should be pointed out that all of the stillbirths occurred before the fortieth week of gestation.

One other clinical problem was troublesome—shoulder dystocia. It was common (13 per cent incidence) and caused the death of 1 baby and damage to 3 others. A more liberal use of cesarean section would have prevented this but at what maternal hazard? Half of these patients are obese, many are extremely obese, and as such are poor candidates for surgery. The only death in approximately 600 consecutive cesarean sections during the past five years occurred in an obese diabetic mother with a bad obstetrical history and an excessively large infant.

Cesarean section is wisely chosen in the woman who has a history of dystocia. It should be considered in the presence of a small or borderline pelvis and in any pelvis having some narrowing of the anteroposterior diameter. Especially undesirable is the flat or the android pelvis and the pelvis with some type of anteroposterior projection of the sacrum.

If vaginal delivery is chosen, trouble can be avoided if it is anticipated. Whatever method of anesthesia is used must give complete muscular relaxation of the vagina and perineum. This, coupled with a generous mediolateral episiotomy and a knowledge of the technique of shoulder delivery, is essential.

Postpartum hemorrhage commonly observed in such patients can be prevented. It is departmental policy to have blood immediately at hand for all patients suspected of postpartum hemorrhage. Prior to delivery infusion of 1 L. of 5 per cent dextrose is started intravenously through an 18 gauge needle. As soon as the placenta has been delivered 2 ampules of ergonovine ($\frac{1}{160}$ grains or 0.4 mg.) are added to the infusion which is allowed to flow in during the next two hours. We have found this to be an extremely effective method of preventing postpartal uterine atony.

Years will be required to show which of these patients ultimately become diabetic. However, we should point out that two unrecognized cases of diabetes were discovered by the study. Even more important is recognition of the triad of big babies, obesity, and abnormal glucose tolerance. All mothers with this triad are candidates for diabetes but not all will be elected. It is in this group that prophylaxis in the form of rigid measures for reduction of weight are of paramount importance.

Conclusions

1. Two changes in carbohydrate metabolism may occur during pregnancy:

(1) Renal threshold is altered in approximately half of all normal pregnancies; it is lowered in 30 per cent and elevated in 20 per cent. (2) Glucose tolerance curves are elevated abnormally in 8 per cent of normal pregnancies. However, there seems to be no correlation between the two.

2. Quantitative urine sugar determinations done upon fasting specimens reveal that 10 per cent of all normal patients spill a trace of sugar during pregnancy. To be of clinical value tests for sugar should be done upon fasting specimens.

3. Fermentation studies indicate that the blood normally contains about 8 mg. per cent of nonfermentable substances. No clinical importance could be determined.

4. During normal pregnancy the glucose tolerance curve falls slightly, but in 8 per cent of the mothers it rises and appears to be diabetic. If the mother has given birth to an excessively large baby the curve is elevated nearly half of the time.

5. As a rule these elevated curves begin to fall immediately after delivery and ultimately return to normal. In some patients the curve rises after delivery. These women probably have unrecognized diabetes mellitus.

6. The triad of abnormal glucose tolerance, maternal obesity, and excessively large infants is clearly established.

7. The data suggest that no arbitrarily set weight constitutes excessive size. On the basis of abnormal glucose tolerance a minimum weight of 4,000 grams is probably correct while on the basis of dystocia a minimum weight of 5,000 grams is more accurate.

8. Administration of cortisone to the normally pregnant woman will produce intolerance to glucose as manifested by a 20 to 25 per cent elevation of the glucose tolerance curve. This suggests that hormones and not nutrition may be responsible for at least some excessive fetal size.

9. Several clinical problems are found. Toxemia, shoulder dystocia, and antepartal fetal death are common, as well as serious complications in the mothers of excessively large babies.

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Discussion

DR. LUCIEN R. PYLE, Topeka, Kan.—The paper of Dr. Lund and Dr. Weese covers a field of original research in a hitherto unexplored field in intrauterine nutrition of the infant. Every bit of experimental and clinical evidence that can be added to our meager knowledge in this field will lead to an improvement in fetal salvage and a decrease in maternal complications. Certainly, the balance of nutrition from spermatogenesis, ovulation, fertilization, and through the period of growth, controls to a degree the quality of the mature product. It is with that thought in mind that I shall discuss this presentation.

The single animal cell is quite dependent upon its environment for its nutrition. It absorbs its food elements by simple osmosis, probably of a gradient nature but altered somewhat by the selectivity of the cell membrane. The ovum, incubated at a favorable temperature and bathed in the tissue fluids of its progenitor, can functionally survive for a period of 12 to 24 hours. The spermatozoa cannot survive for a much longer period. However, after these cells unite, their life span is trebled. After growth and specialization of tissue have begun, the organism is safeguarded by a multitude of automatic integrated processes.

Certain questions entered my mind as I read Dr. Lund's paper, and although he suggests some of the answers in his cortisone series, his comment, and conclusions, further and more widely dispersed research will have to be carried on before the answers are apparent. Is the baby large because of the increased glucose tolerance curve? If so, how do we explain that in his series only 14.5 per cent of diabetic mothers gave birth to large babies? Other investigators report an incidence as high as 25 per cent. Is it some peculiar selectivity of absorption in the placenta that gives 75 to 85 per cent of the babies of diabetic mothers a near average birth weight, and a lack of selectivity that permits the other 15 to 25 per cent to become large babies? Since in the authors' series an obese mother, with or without an altered glucose tolerance curve, was more prone to produce a big baby than her lean sister, can we attribute the large baby to an altered glucose tolerance curve, a chronic alimentary hyperglycemia from overeating, some underlying cause in the inherent characteristics of the individual, or to variations from normal in the hormonal pattern of the mother, the baby, or both?

According to DeLee's textbook, "the interchange of gases, water, and nourishment takes place through the wall of the villus by osmosis and by vital action of the cells themselves, particularly the latter." Hamblen, in discussing the reciprocities of the fetal and the maternal pancreas, says that glucose filters across the placental barrier from the maternal reservoirs but that this simple filtration process is only one of the many factors involved. According to other investigators, some of the substances which cross the placental barrier which may have an influence upon fetal growth and development are thyroglobulin or its iodine-containing congeners and the placental and chorioplacental hormones. Whether insulin, the pituitary hormones, or the adrenal hormones cross the placental barrier is not definitely known. Certainly it must be a combination of all of these factors that controls the size of a baby born at term.

The weight of a newborn infant is dependent upon its general musculoskeletal development and the overlying fatty deposit, considering of course that there is a normal electrolyte and fluid balance. I have delivered babies light in weight, small of frame, and short in stature who had a liberal deposit and adequate distribution of adipose tissue. But I can

well remember two male infants, born of a 6 foot mother and a 6 foot, 7 inch father, weighing 11 and something over 12 pounds, that were quite free of adipose tissue. They both offered problems in the delivery of the shoulders.

To illustrate my point, I checked the records of our last 136 babies born at term in one hospital, and I have prepared three tables which show the variations in weight and stature. Although the series is too small for complete evidence, it is sufficiently large to show certain trends. Table I shows that as the average length of the baby increases inch by inch, the average weight goes up more rapidly.

TABLE I. LENGTH AND WEIGHT

LENGTH	NUMBER OF BABIES	WEIGHT
19 inches	25	6 pounds, 7½ ounces
20 inches	49	7 pounds, 4⅓ ounces
21 inches	48	7 pounds, 15 ounces
22 inches	14	8 pounds, 14½ ounces
	136	7 pounds, 7.6 ounces (average)

Table II shows that in each weight category, as the length of the babies increases, the weight gradually goes up.

TABLE II

GROUPS BY WEIGHT	NUMBER OF BABIES	LENGTH	AVERAGE WEIGHT
Under 7 pounds	21	19 inches	6 pounds, 4½ ounces
	14	20 inches	6 pounds, 7⅝ ounces
	3	21 inches	6 pounds, 9 ounces
7 to 8 pounds	4	19 inches	7 pounds, 6 ounces
	29	20 inches	7 pounds, 7⅓ ounces
	27	21 inches	7 pounds, 9 ounces
8 to 10 pounds		19 inches	
	6	20 inches	8 pounds, 6 ounces
	18	21 inches	8 pounds, 11½ ounces
	14	22 inches	8 pounds, 14½ ounces
	136		7 pounds, 6 ounces

Table III is an attempt to correlate the size of the mother and her weight gain during pregnancy with the weight of the newborn. This table to a degree confirms Dr. Lund's statement that obese mothers have large babies. However, it is interesting to note that in the 150 to 175 pound class those mothers we would classify as distinctly overweight for their height made smaller weight gains and had smaller babies than those women we would classify as large women and not particularly overweight. As Dr. Lund has stated, there seems to be no correlation between infant size and the mother's weight gain during pregnancy.

TABLE III

			NET GAIN OF MOTHER (POUNDS)			WEIGHT OF BABIES (POUNDS)		
		NUMBER	GREATEST GAIN	SMALLEST GAIN	AVERAGE	GREATEST	SMALLEST	AVERAGE
Over 185 pounds	Obese	9	40	16	29 plus	9-13	7-2	8-9
	About average	2	33	27	30	9-1	7-10	8-5
150-175 pounds	Obese	9	31	0	15	8-5	6-3	7-10
	About average	32	35	10	23 plus	10-13	6	7-14
To 150 pounds	Gained 30 pounds	12	40	30	32	8-4	6-11	7-8
	Gained 20-30 pounds	34	28	20	23 plus	9-10	5-1	7-5
	Gained 10-20 pounds	14	19	6	15	8	6-2	7

The authors' cortisone series suggests that the occurrence of an abnormal glucose tolerance curve during pregnancy might stem from increased adrenal activity and its resultant diabetogenic trends.

The routine use of fasting blood sugar determinations and glucose tolerance determinations when indicated during the third trimester of pregnancy could well give us some useful and interesting information.

May I reiterate that the questions I have raised were not advanced in any way to detract from the authors' careful research and careful reporting. They were raised to emphasize that fetal growth and development are governed by a complex process with many ramifications and variations. An abnormal glucose tolerance curve is just one of the ramifications.

DR. RALPH A. REIS, Chicago, Ill.—Dr. Lund set out to review and extend the studies on glucose tolerance in normal pregnancy and to correlate abnormal glucose tolerance curves with obesity and with large babies. The cause of abnormal glucose tolerance curves is discussed. The triad of obesity, abnormal glucose tolerance curve, and large babies has been well established by this report. Intolerance to glucose produced by cortisone during pregnancy has substantiated the work that has been done previously by others.

This triad of obesity, abnormal glucose tolerance curves, and large babies is important. It raises the question whether all obese women should have a glucose tolerance curve during the last trimester. Furthermore, if the curve is found to be abnormal and an oversized baby is suspected, might it not be well for us to consider managing these women in the last trimester as though they actually had diabetes. I think if this had been done in Dr. Lund's series, 4 of the 5 intrauterine fetal deaths might have been avoided. He states that the incidence of large babies is much greater in this group with obesity and abnormal glucose tolerance curves than in his diabetic women. I wonder how much of that is due to the extra care the diabetic woman gets and the more or less studied obstetric neglect of this group showing the triad under discussion.

There is one small but very interesting sidelight of this problem. Dr. Lund shows that the glucose tolerance curve returns to normal on the second postpartum day. I think we may draw reassurance from this in another direction, namely, that modern anesthesia does not inhibit or damage the liver as much as we have heretofore believed. For, if the liver were affected by the anesthesia of delivery, the glucose tolerance curve could not possibly return to normal by the second postpartum day.

A discussant must have some points of difference. Is the abnormal glucose tolerance curve which persists the forerunner of true diabetes? When we have an abnormal glucose tolerance curve, abnormal blood sugar level, and what Dr. Lund has called "just a low renal threshold," the question of whether that is or is not true diabetes, or the forerunner of true diabetes, becomes very important. Our internists feel, for example, that a very obese man with hyperglycemia and glycosuria and, therefore, a true diabetic, can, if he is reduced by 100 pounds, lose his hyperglycemia and lose his glycosuria. Can we say this man did not have diabetes under the strain of the obesity? No—he had diabetes which disappeared when the obesity disappeared. So I have the feeling that many of these patients are diabetics, or potential diabetics, under the strain of pregnancy, and that, with the termination of the pregnancy, with its altered physiology of liver, pancreas, pituitary, adrenal, and whatever else may be involved, the diabetes disappears temporarily. I feel, however, that many of these women will have diabetes in the years to come. I would like to have Dr. Lund come back about 20 years from now, and tell us how many of these women actually became true diabetics.

Last, he was a little bit disappointed in the high incidence of what he terms "flat glucose tolerance curves" and the "delayed glucose tolerance curve." He did not find as many sharp rises as he expected. How much of this was due to the tension state of the procedure involved, and how much was due to slow absorption and delayed gastric motility so characteristic of pregnancy during the last trimester? I think he would have found many more had he used a group of tolerance tests which depended upon the intravenous administration of glucose. It seems to us that this is a much more accurate way of determining glucose tolerance. I

feel that it should have been used and it is the method that I would recommend to Dr. Lund if he continues this work.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—It is very appropriate to bear in mind that in using any biological process, including yeast fermentation, one must keep all factors as nearly constant as possible. Yeasts are nonpathogenic organisms. The species in question is *Saccharomyces cerevisiae*. These organisms are totally unrelated to the medical Monilia or *Candida albicans*. Perhaps Fleischmann yeast has a slightly greater concentration of organism per volume than does Red Star. Both companies make a very serious effort to keep their strains standard. Their special problem is to maintain an unchanged metabolic action and avoid the development of mutations and also to prevent contamination by other fungi. A point on fermentation is that the size of the inoculum is related to the amount and rapidity of gas and acid production. The gas may escape in a few hours without detection and the acidity can be reversed spontaneously by loss of the acid into the room air. For accuracy one should count the organisms per unit measure periodically. Also one should use yeast sources of definite age. A rapidly growing culture in broth is a good source for inoculum, but this source is more laborious and presents certain pitfalls. For this type of study it is probably better to use a commercial yeast source. These yeasts are grown in conditions free from other organisms, but once the foil is opened it may be attacked by other fungi as well as bacteria which can give a false response in tests. These foils are dated in code.

Either of these companies should be willing to cooperate with the essayists and their colleagues for a scientific study. The older the foil, the less active it may be. Therefore, there are several factors not unlike those found in the use of mice or rats for test purposes.

DR. JAMES E. DAVIS, Dexter, Mich.—It is appropriate to cite a case which will illustrate in repeated pregnancies some of the clinical features of glucose tolerance with obesity in both parents. The mother, who weighed 235 pounds, gave birth to her first child when 18 years of age. In each of the first six months of the first pregnancy, free flowing occurred at the time of her menstrual cycles and uterine pains threatened loss of the fetus. Rest and sedative medication were unsuccessful and miscarriage occurred in the sixth month. In each of 4 succeeding pregnancies the patient came under my care.

I told the patient I felt sure the probable cause of her predisposition to abort and miscarry was related to her obesity and that of her husband, who weighed 215 pounds, making their combined weight 450 pounds. Also, I informed her that frequent testings of the urine would be required and ovarian function should be supplemented. Flowing came on in the second month of her second pregnancy. Lipolutein was promptly given. The pains and the flowing quickly subsided and in each of the following months the same results were attained. Delivery of a healthy 10¼ pound baby came at term.

In the following three years 3 additional successful deliveries were made. All 4 babies weighed over 10 pounds each at delivery. All 4 were well nourished, healthy, large, and strong.

Medication during the last 3 pregnancies was changed to alpha-tocopherol acetate. During the fifth pregnancy no flowing and no uterine pains appeared.

In the mother a lowered threshold for carbohydrate was temporarily present, giving a trace of sugar in the urine.

The father has had a distinct trace of sugar in the urine and is now on an antidiabetic diet.

DR. LUND (Closing).—What causes big babies we do not know. Heredity plays a part, perhaps hormonal influence plays a part. Are these women prediabetics? We have no idea. So it is with some regret, then, that we leave you with most of these questions unanswered and yet perhaps this investigation has opened the way for further considerations and study in your own medical practice.

THE EFFECT ON SODIUM EXCRETION OF TREATMENT DRUGS USED IN PREGNANCY TOXEMIA*

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THE significance of the sodium ion in the production of some pregnancy toxemias is well known. The metabolism of this important electrolyte in this condition is, however, not too clearly understood. Sodium metabolism is often referred to as salt metabolism, the two terms being used interchangeably and with synonymous implications. While the sodium ion behaves in a certain fashion, it does not always explain the metabolism of sodium chloride as a molecule. Since sodium comprises 40 per cent of the sodium chloride molecule, we cannot conclude that the metabolism of sodium in the body is 40 per cent that of sodium chloride. Neither may we conclude that the metabolism of sodium equals that of chloride. It would thus seem that our consideration of sodium metabolism as it relates to the toxemias of pregnancy needs re-evaluation.

Since there seems to exist some relationship between the circulation in general, the renal apparatus, and the metabolism of sodium in pregnancy toxemias, there also exists a need for clarification of some of the factors involved in the process of excretion in this important electrolyte. While it is generally considered that renal excretion of sodium is proportionate to water excretion, the interrelationships of such activity have not been fully studied in the patient with pregnancy toxemia. This considered proportionate relationship between water metabolism and sodium excretion has formed the basis for some treatment methods used in the toxemias of pregnancy.

That the renal epithelium in the proximal portion of the proximal tubules accounts for most of the reabsorption of water when the concentration of plasma is normal, is a well-known fact. Whether these same conditions operate in a patient with pregnancy toxemia has not been clarified, particularly where the pattern of arteriolar spasm for varying periods of time must be considered.

Just as proximal tubular reabsorption of water occurs, so is there little doubt that the reabsorption of most electrolytes is likewise carried out in the proximal renal tubules. The reabsorption of sodium and water does occur primarily in the proximal tubule. It has been shown by Wesson and coworkers[1, 2] that the reabsorption of water and of electrolytes is not proportionate. They noted that as much as 65 per cent of the water of the glomerular filtrate was being excreted in the urine at a time when only 13 per cent to 17 per cent of the filtered sodium was excreted.

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Distal tubular reabsorption of water occurs only under the influence of antidiuretic substance. Where electrolyte concentration is *increased,* the osmotic pressure of the plasma is also increased, stimulating the posterior pituitary to increase its secretion of more antidiuretic substance, thus increasing the rate of distal tubular water reabsorption. Through this mechanism of increased reabsorption, water excretion is reduced with a return of more water to the plasma to reduce plasma concentration. Where *decreased* electrolyte concentration exists, there also exists decreased osmotic pressure because of an excess of water. As a result, not as much hormone is secreted, with a consequent decrease in the amount of water reabsorbed. Thus, more water is excreted in the urine. In this way, the plasma water is removed, and thus increases the electrolyte concentration and thereby the osmotic pressure of the tubular fluid.

Methods and Materials

In order to determine some of the features of sodium metabolism, 36 hospitalized patients with the diagnosis of pre-eclampsia were studied. The final diagnosis of this type of toxemia was based upon antepartum, intrapartum, and postpartum information, as well as upon data obtained during the pregravid period and after the puerperium. Each patient in the group was studied under similar circumstances, each patient being given 17 Gm. of sodium chloride during the 48 hours immediately prior to the study.

All patients were studied under fasting conditions. Into one antecubital vein inulin and para-aminohippuric acid were introduced by means of a constant infusion pump, at a rate of 1 c.c. per minute, after a priming dose of 30 c.c. of 10 per cent inulin. Five per cent glucose in distilled water was injected into the other antecubital vein, in order to maintain "an open vein" so that blood could be drawn at the end of each study period. Glomerular filtration rates were studied in our patients by the use of constant infusion, thus maintaining a constant plasma level of inulin. In this way the concentrations in arterial and venous blood are rendered identical, since the venous blood receives the inulin at a rate equal to that at which it is being excreted by the kidney. A period of equilibration of 40 minutes was carried out on all patients before any measurements were actually made. Six control periods of 20 minutes each were used in each patient. The average of these six control periods is represented as the zero line in the figures here presented. Each bar represents one patient, and in these figures the direction of the bar from the zero line represents the increase or decrease of the various factors studied, which are expressed in percentages. These results represent the average of six test periods of 20 minutes each following the administration of the drugs utilized. The drugs used were, for the most part, those commonly used or which have been used in the treatment of pregnancy toxemia. Other drugs utilized were of interest as they relate to sodium and water metabolism and their effect upon the various factors considered important in the pregnancy toxemias. These test drugs were classified as sedatives, diuretics, fluids, and antihypertensive agents. Each drug was administered in the same manner and dosage as that used in the treatment of pregnancy toxemias. All experimental methods and calculations were standard in each patient.

Up to a very few years ago, the analytical methods for sodium were unduly laborious, prolonged, and encumbered with marked inaccuracy. Because of this, sodium metabolism was usually interpreted in terms of chloride metabolism or even with the mistaken designation of sodium chloride metabolism represented as a physiologic unit. In our study all measurements for sodium were performed in duplicate, using the Beckman Flame Spectrophotometer.

In addition to measurements of the glomerular filtration rate of water, renal plasma flow, and urinary volume, determinations of sodium excretion, sodium concentration, glomerular filtration rates of sodium, and tubular rejection fraction of sodium were made.

Sodium Excretion

Even though sodium is excreted through the skin and the gastrointestinal tract, sodium excretion is primarily a renal process and represents the amount of the cation filtered at the glomerulus minus the amount reabsorbed by the tubules. Sodium excretion is influenced by several factors: (1) the glomerular filtration rate, (2) concentration of sodium in the plasma, (3) antidiuretic substance, and (4) the tubular rejection fraction of sodium. In addition to these, the action of the adrenal cortical hormones or any factors influencing their secretion affect sodium excretion.

Since the excretion of this electrolyte depends, for the most part, upon sodium concentration, these two will be considered simultaneously. Where the concentration of sodium in the plasma is decreased, a decrease in sodium excretion would result. This, however, depends upon the condition of the proximal tubules. As a result of such depression of electrolyte concentration, a decrease in the oncotic pressure of the plasma would exist and thus a decrease in tubular reabsorption of sodium. Where the excretion of water differs from that of sodium this would seem to indicate an independence of reabsorption of sodium from that of water in the proximal tubules. Wesson and associates have shown that sodium reabsorption is an active process rather than a process involving passive diffusion of sodium along with whatever water is reabsorbed.

Relman and collaborators[3] showed that mannitol and glucose osmotic diuresis, induced simultaneously with copious water diuresis, increases sodium and chloride excretion. The simplest interpretation is that osmotic diuresis sweeps sodium out of the proximal tubule faster than the distal tubule can handle it; this sodium appears in the urine irrespective of the rate of distal tubular water reabsorption.[4]

In addition to mannitol and glucose osmotic diuresis, the excretion of sodium can also be reduced by the dilution of sodium in the proximal tubule, as shown by Wesson, as well as being influenced by the sodium load, as shown by Green and Farah,[5] as well as in our present study.

Sodium reabsorption is also thought to occur in the distal tubule. The amount of this function carried out distally depends upon the relative amount absorbed proximally. It is generally considered that 12 per cent of the water filtered is available to the distal tubule for reabsorption; likewise a similar amount of sodium is also available for distal reabsorption. It would seem to me that this would operate in the toxemias of pregnancy, where, with mild arteriolar spasm producing only glomerular damage and proximal damage of the tubule, in the early phases (which *may* heal), we might expect to get large volumes of dilute urine with an increased excretion of sodium. This would occur because of the decreased ability of the proximal tubular epithelium to carry out adequate reabsorption of either water or sodium. We would also expect that such an occurrence would come about because the volume of water and electrolyte placed for reabsorption by the distal tubule would be so great as to place an undue load on the distal tubular epithelium.

Glomerular Filtration Rate of Sodium

The glomerular filtration rate of water follows a fairly constant level in normal subjects, averaging approximately 120 c.c. to 130 c.c. per minute. In pregnancy toxemia this figure is lowered, as has been shown by us[6] and other observers,[7, 8, 9, 10] to vary from 85 c.c. to 102 c.c. per minute, or lower. The

filtration rate of water seems to depend particularly upon the extracellular fluid volume and the state of hydration of the individual. When the extracellular fluid volume is contracted, a decrease in glomerular filtration rate occurs with very high urine flows. Where excessive hydration exists, the filtration rate is above normal, probably because of the increased extracellular fluid volume. The antidiuretic hormone controls urine flow independently of the filtration rate by its regulation of the quantity of water reabsorbed by the renal tubules, regardless of the filtration rate. Among a series of normal pregnant patients we found the average glomerular filtration rate of sodium to be 18.7 meq. per cubic centimeter per 1.73 sq. M. of body surface.

As we have stated, the renal excretion of sodium is influenced by how slowly or how rapidly the sodium is filtered. When the rate is slowed, there is ample opportunity for greater reabsorption; this is not usually possible when the filtration rates are high.

Tubular Rejection Fraction of Sodium

This fraction of sodium is that portion of filtered sodium which does not undergo tubular reabsorption. It represents the amount of sodium filtered by the glomerulus as related to the filtered fraction which does not undergo tubular reabsorption. It is represented as the number of milliequivalents of sodium excreted per 100 meq. filtered, and is thus expressed in percentage. Green and Farah[5] found that, in the presence of low filtration rates, the amount of filtered sodium excreted increased correspondingly in the presence of a constant plasma concentration. They noted a high correlation between the rate of sodium excretion and the percentage of filtered sodium excreted. This we shall show in presenting the effect of saline as the test drug where a high correlation was found between the rate of sodium excretion and the amount of sodium introduced.

Sedatives

Among the sedative preparations used by us to determine their effect upon sodium excretion were chloral hydrate, Demerol, magnesium sulfate, paraldehyde, and morphine (Fig. 1). These test drugs have all been used for their sedative action in the treatment of pregnancy toxemia. It will be noted in Fig. 1, that sodium excretion, following the administration of sedatives as a group, is quite generally decreased with the smallest average decrease being among those patients receiving paraldehyde, whereas the greatest diminution in excretion occurred among those receiving Demerol. This is consistent with findings previously reported by us, in a study relative to the effect of Demerol on urinary output alone.[11]

It was found in this group of patients receiving sedatives that, in general, a relatively marked increase in renal plasma flow occurred, except among the groups receiving chloral hydrate and Demerol, where the decreases compared with the control average varied up to 26 per cent and 22 per cent, respectively, lower than the control average. It is interesting to note that where the greatest decrease in glomerular filtration rate of sodium occurred, namely, with Demerol, the sodium excretion was most markedly depressed, and also that where the glomerular filtration rate of sodium was not so markedly depressed following the use of the test drug, the change in sodium excretion was relatively less pronounced than otherwise noted.

The concentration of sodium was most markedly increased following the use of chloral hydrate where a high of 316 per cent increase was associated with a 66 per cent decrease in the urinary volume. Similar findings occurred with Demerol, as we have shown. It is to be noted that, with the use of morphine, the most pronounced decrease in sodium concentration occurred. This occurred

in every instance where morphine was used, and is as would be expected, since in a previous study it was noted that morphine, at least in patients with toxemia of pregnancy, was diuretic in 72 per cent of the cases so tested. Associated with this was an almost proportionate increase in the glomerular filtration rate of sodium above the control average, and a general increase in urinary volume.

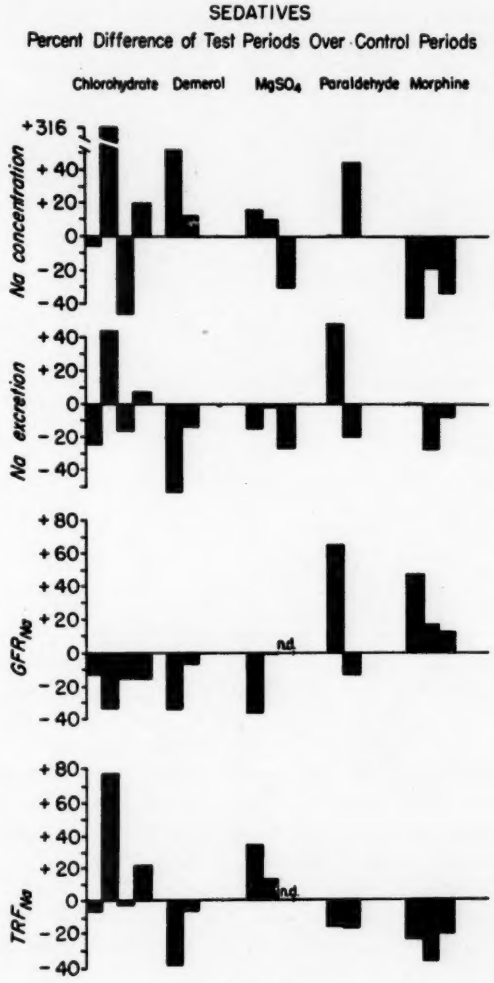

Fig. 1.

Magnesium sulfate, in each instance where it was used, was associated with a decrease in sodium excretion as compared to the control average, but with relatively small comparative change, varying from a decrease of 1 to 27 per cent below the control average. In one instance, along with this decrease in sodium excretion, sodium concentration was likewise decreased in the presence of an increase in the urinary output of 4 per cent above that of the control average, and an associated and very marked increase in the glomerular filtration rate of water and renal plasma flow.

In Table I, the relative changes are noted following the testing with each drug with particular reference to the response of sodium excretion as compared to the control periods. For example, where chloral hydrate was used and an

increase in sodium excretion attained, an increase in sodium concentration of the urine occurred due to an increase in the tubular rejection fraction of sodium. These changes were associated with a decrease of the urinary output, renal plasma flow, glomerular filtration rate, the glomerular filtration rate of sodium, and the tubular rejection fraction of water. The correlated changes as compared with the response of sodium excretion are shown in the table.

TABLE I. SODIUM EXCRETION RESPONSE IN PRE-ECLAMPTIC PATIENTS TESTED WITH SEDATIVES

AGENT	NUMBER OF CASES	RESPONSE OF SODIUM EXCRETION		URINE OUTPUT	RENAL PLASMA FLOW	GLOMERULAR FILTRATION RATE	GLOMERULAR FILTRATION RATE OF SODIUM	SODIUM CONCENTRATION	TUBULAR REJECTION FRACTION OF WATER	TUBULAR REJECTION FRACTION OF SODIUM
Chloralhydrate	4	Increased	2	–	–	–	–	+	–	+
		Decreased	2	+	+	–	–	–	+	–
Demerol	2	Increased	0							
		Decreased	2	–	–	–	–	+	–	–
Magnesium sulfate	3	Increased	0							
		Decreased	3	–	+	+	–	–	–	+
Paraldehyde	2	Increased	1	+	+	+	+	no change	–	–
		Decreased	1	–	+	–	–	+	–	–
Morphine	3	Increased	1	+	+	+	+	–	+	–
		Decreased	2	+	+	+	+	–	+	–

Diuretics

Two diuretics were used in this study, aminophylline and Mercuhydrin, both of which are well-known powerful diuretics (Fig. 2). In each instance, the general trend was an increase in all factors studied, as compared to the average of the control values. Where aminophylline was used, the urine volume increased 116 per cent above that of the control, with corresponding increases in the glomerular filtration rate and renal plasma flow. However, there was a sharp decrease in sodium excretion with a 77 per cent drop below that of the control average. It might thus be emphasized that, while aminophylline is a powerful water diuretic, at least in the one instance studied by us, its action markedly reduced the output of sodium, which might best be explained on the basis of the resulting osmotic diuresis.

Where Mercuhydrin was used, a mild antidiuretic effect occurred in one patient of 15 per cent less than the control average, while in the other patient urinary output increased to 75 per cent beyond that of the control average. In each instance, there was a sharp decrease in sodium excretion of 90 to 136 per cent, respectively, associated with a marked increase in the sodium concentration and in the tubular rejection fraction of sodium. It would appear that, in considering the underlying factor of decreasing the extracellular space, mercurial diuretics are more effective in maintaining such a decrease than are the xanthines where only fluid rather than sodium is excreted.

Fluids

Fluids of various composition and concentration have been used in the management of pregnancy toxemia for years. We, in our study, evaluated those fluids about which there has been considerable interest relative to diuresis.

Among this group, six patients were studied; 50 per cent glucose, plasma, and isotonic saline were administered to two patients each as the test drug.

Fifty Per Cent Glucose.—In our published study on the effect of renal output, we noted that hypertonic glucose resulted in a decrease of urinary output in the majority of patients. Brown and Bradbury[12] also found that eclamptic patients with oligura or anuria showed no response to the use of 50 per cent glucose. In our two patients in the present study, a decrease in urinary output

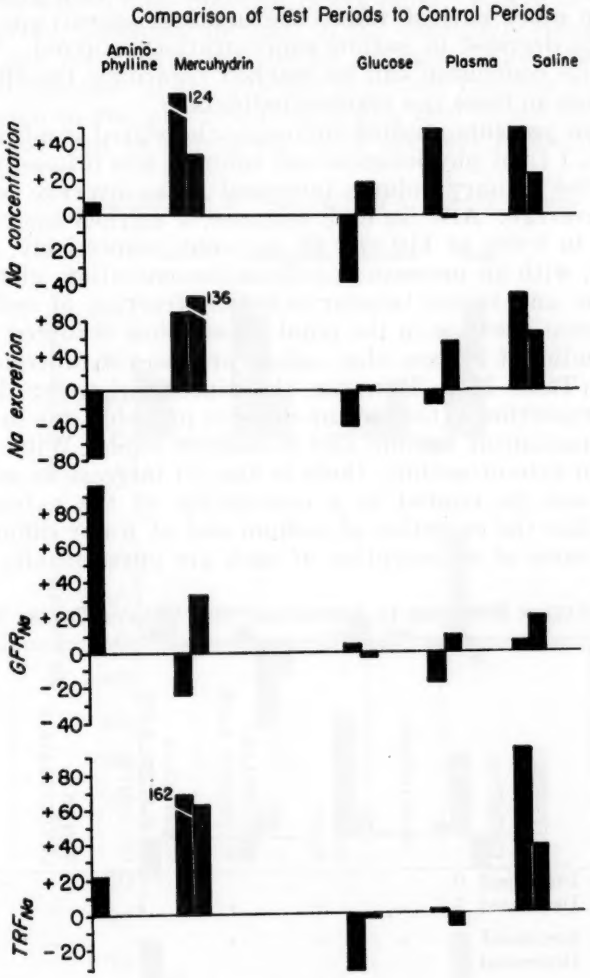

Fig. 2.

also resulted. The output in these patients was 3 per cent and 13 per cent less than the control average. Likewise, sodium excretion showed a variable response following the administration of 50 per cent glucose; one patient presented a decrease in sodium excretion of 40 per cent less than the control average in the first instance, while the other patient showed a minimal increase amounting to 4 per cent above the control average. Both these were associated with negligible responses in the glomerular filtration rate of sodium. An average decrease of 16 per cent in the tubular rejection fraction of sodium resulted following the administration of 50 per cent glucose. We would interpret this latter as representing a trend toward depression of sodium excretion.

Plasma.—Two patients, given 250 c.c. of plasma diluted with an equal volume of salt-free isotonic glucose, showed marked variation in the urinary output. In one instance, the urinary output decreased 43 per cent below the control average, while in the other a 56 per cent increase occurred as related to the control average. In the patient presenting a decreased urinary output, there was an associated decrease in the sodium excretion and in the glomerular filtration rate of sodium, but with an increase in sodium concentration amounting to 49 per cent above the control average. It would appear, in this patient, that the rate of tubular reabsorption of water occurred at a rate greater than that of sodium. In the other patient where the urinary output was markedly increased, a negligible decrease in sodium concentration occurred. Thus it would seem that no definite conclusion can be reached regarding the effect of plasma on sodium metabolism in these two toxemic patients.

Saline.—To two patients studied following the stated conditions of equilibration and control, 1 L. of physiological salt solution was infused intravenously. In each instance, the urinary volume increased to an average of 38 per cent above the control average. Also, in each instance, a marked increase in sodium excretion occurred to levels of 110 and 66 per cent, respectively, above that of the control average, with an increase in sodium concentration, glomerular filtration rate of sodium, and in the tubular rejection fraction of sodium. In one instance, a 0.4 per cent decrease in the renal plasma flow occurred.

From these studies it is seen that saline produces a diuresis of water as well as of sodium (Table II). However, the diuresis of water does not occur in quite as high a proportion as the sodium diuresis probably due to the increased tubular rejection fraction of sodium and to sodium load. With the increased glomerular filtration rate of sodium, there is also an increase in sodium concentration; this may well be related to a contraction of the extracellular fluid volume. The fact that the excretion of sodium and of water differs would lead us to feel that the rates of reabsorption of each are operationally different.

TABLE II. SODIUM EXCRETION RESPONSE IN PRE-ECLAMPTIC PATIENTS TESTED WITH DIURETICS

AGENT	NUMBER OF CASES	RESPONSE OF SODIUM EXCRETION	URINE OUTPUT	RENAL PLASMA FLOW	GLOMERULAR FILTRATION RATE	GLOMERULAR FILTRATION RATE OF SODIUM	SODIUM CONCENTRATION	TUBULAR REJECTION FRACTION OF WATER	TUBULAR REJECTION FRACTION OF SODIUM
Aminophylline	1	Increased 0							
		Decreased 1	+	+	+	+	+	+	+
Mercuhydrin	2	Increased 2	+	−	+	+	+	+	+
		Decreased 0							
Fluids.—									
Glucose	2	Increased 1	−	−	+	−	+	−	−
		Decreased 1	−	+	+	+	−	+	−
Plasma	2	Increased 1	+	+	+	+	−	+	−
		Decreased 1	−	−	−	−	+	−	+
Saline	2	Increased 2	+	+	+	+	+	+	+
		Decreased 0							

Antihypertensive Drugs

While we have included desoxycorticosterone acetate and Metycaine as antihypertensive drugs (Fig. 3), we do so only because of the production of a slight drop in blood pressure which commonly follows the administration of these

agents. DOCA was administered to three patients in dosages of 5 mg. intramuscularly, while Metycaine was given in doses of 22 mg. intrathecally. The dose of Priscoline was 50 mg. intramuscularly, given in two doses 10 minutes apart, while protoveratrine was administered intravenously in a dose of 0.2 mg. following the control period.

DOCA.—Following the administration of DOCA, the urinary volume decreased in each instance, dropping from 13 to 32 per cent below that of the control average. With this, an associated increase of sodium excretion occurred in two instances with a mild decrease in the other. Where an increase in sodium excretion occurred, a marked increase in the electrolyte concentration occurred, averaging 64 per cent above the control average. This was associated with a rather marked increase in the tubular rejection fraction of sodium, but with marked variation in the glomerular filtration rate of sodium, varying from an increase of 4 per cent to a decrease of 20 per cent below the control average.

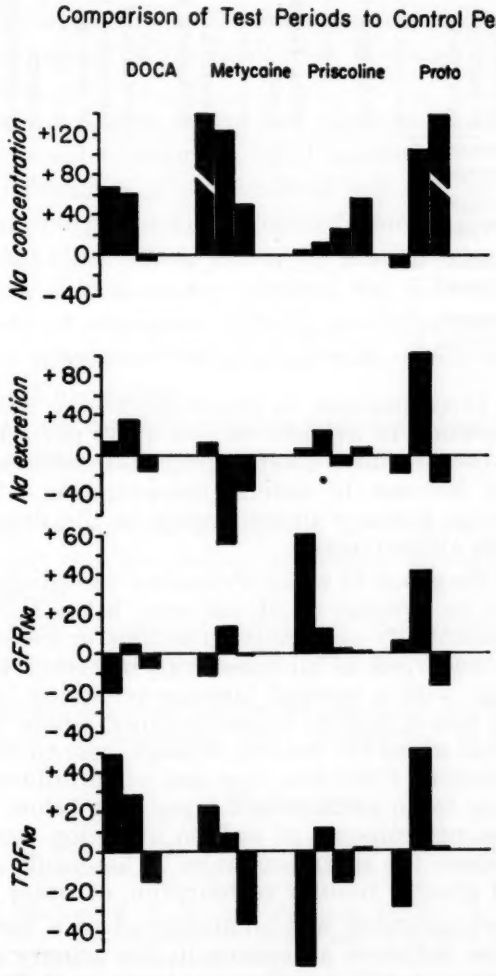

Fig. 3.

Where the sodium excretion was decreased with the use of DOCA, it decreased to 18 per cent below the control average and was associated with a decrease in sodium excretion, glomerular filtration rate of sodium, and tubular rejection fraction of sodium. Where urine volume was decreased most sharply, the renal

blood flow was also likewise decreased, but, in the other two instances where a slight decrease in urinary output occurred, there was an increase in renal plasma flow.

It will be seen (Table III), among this group of pre-eclamptic patients, that DOCA did not promote tubular reabsorption of sodium as in normal patients, but rather produced a decrease in sodium retention in two of our patients. In the other patient, the usually anticipated phenomenon of increased tubular reabsorption with a decrease of sodium excretion occurred. However, in all instances increased tubular reabsorption of water was manifest.

TABLE III. SODIUM EXCRETION RESPONSE IN PRE-ECLAMPTIC PATIENTS TESTED WITH HYPOTENSIVE AGENTS

AGENT	NUMBER OF CASES	RESPONSE OF SODIUM EXCRETION	URINE OUTPUT	RENAL PLASMA FLOW	GLOMERULAR FILTRATION RATE	GLOMERULAR FILTRATION RATE OF SODIUM	SODIUM CONCENTRATION	TUBULAR REJECTION FRACTION OF WATER	TUBULAR REJECTION FRACTION OF SODIUM
Doca	3	Increased 2	–	–	–	–	+	–	+
		Decreased 1	–	+	–	–	–	–	–
Metycaine	3	Increased 1	–	–	–	–	+	–	+
		Decreased 2	–	+	+	+	+	–	–
Priscoline	4	Increased 3	–	+	+	+	+	–	–
		Decreased 1	–	–	+	+	+	–	–
Protoveratrine	3	Increased 1	–	+	+	+	+	–	+
		Decreased 2	–	–	–	–	+	–	–

Metycaine.—In the three patients to whom Metycaine was given, the net result was an average decrease in urinary volume of 39 per cent below that of the control average. In two instances a very sharp decrease in sodium excretion occurred with a marked increase in sodium concentration. The decrease in sodium excretion was in no instance proportionate to the decrease in urinary volume which occurred in all instances.

Priscoline.—Among the group to whom Priscoline was administered, urinary volume was decreased to an average of 31 per cent below that of the control periods associated with essentially no change in sodium excretion. An increase of sodium concentration occurred in all cases, varying from 4 to 58 per cent above the control average, with a marked increase occurring in two instances. The glomerular filtration rate of sodium in one instance, where the urine volume was increased to 5 per cent above the control average, rose to 60 per cent. The general trend noted following Priscoline was one of antidiuresis of water of minimal degree amounting to an average of 7.5 per cent below that of the control average, whereas the net response of sodium excretion was one of sodium diuresis of 26 per cent above the control average. This would seem to indicate an operational change of greater tubular reabsorption of water than of sodium.

Protoveratrine.—Protoveratrine was administered as a test drug to three patients. In each of these instances a decrease in the urinary output occurred varying from 2 to 76 per cent with an average decrease of 42 per cent below that of the control periods. Where the smallest decrease in urinary volume occurred, sodium excretion was most pronounced. Where the sharpest decrease in urinary volume occurred, the greatest decrease in sodium excretion occurred; in this instance, the sodium concentration was most marked, reaching a level

of 202 per cent increase above that of the control average. This would seem to reflect that protoveratrine exerts a much greater effect in depressing urinary volume than in depressing sodium reabsorption, particularly in view of the fact that there was a depression of the glomerular filtration rate of sodium in this instance.

Summary and Conclusions

1. Our study seems to indicate that, among the sedative drugs, Demerol, magnesium sulfate, and morphine tend to increase sodium retention. This effect is most pronounced with Demerol and with magnesium sulfate, with relatively mild retention following the use of morphine.

2. In general, the mercurial and xanthine diuretics increased the tubular rejection fraction of sodium and, on the basis of our data, may also be classified as sodium diuretics.

3. No definite statement can be made relative to 50 per cent glucose, except that the trend following its administration is one of water retention as well as of sodium retention.

4. The effects of plasma in the two patients to whom it was administered were so variable as not to permit a valid conclusion.

5. The administration of physiological salt solution was associated with an increase in urinary output and of all other factors studied in sodium metabolism. It would seem that these effects should be considered only as immediate effects and these results should in no way condone the universal administration of salt solution to toxemia of pregnancy patients, nor to pregnancy patients in general.

6. DOCA, in pregnancy toxemia patients, while antidiuretic, tends to enhance the excretion of sodium.

7. In general, the antihypertensive agents studied by us provoke a depression of urinary volume with each agent, but with variable response in sodium excretion.

8. Metabolism of chloride should not be interpreted as the metabolism of sodium, nor should the metabolism of sodium chloride be confused with the metabolism of sodium.

9. In pregnancy toxemia, it seems that the response to various agents reflects operationally different metabolic processes for sodium and for water.

We wish to acknowledge with thanks the generosity of Mr. R. J. Coleman of the U. S. Standard Products Co., of Woodworth, Wis., in supplying us with the inulin used in this study.

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Discussion

DR. WILLIS E. BROWN, Little Rock, Ark.—While there are minor deviations in the techniques employed by Dr. de Alvarez and his co-workers, and certain minor changes in their pattern of investigation, the information which he has presented confirms basically what we had observed previously regarding the effect of various agents on the clinical picture of toxemia of pregnancy.

Three years ago Dr. Conrad Collins in opening the discussion of my paper on this subject, said, in effect, "Now that Dr. Brown has moved to the eclamptic belt, we will be interested to see what he learns there." We have learned a great deal about eclampsia in a very short time for it has been our privilege to see 57 cases of eclampsia in three years. I thought perhaps you might be interested in some rather general observations which we have made.

We began a clinical study with the concept that perhaps if we could reverse water retention by mobilizing and excreting the edema (sodium and water), if we could lower the hypertension, if we could control the cerebral irritability, perhaps the disease or syndrome of eclampsia could likewise be controlled.

We undertook to mobilize and excrete sodium and water by mercurial diuretics and other agents in a manner similar to that presented by Dr. de Alvarez. I am sorry to say that despite the fact that we have in many eclamptic patients removed as much as 30 pounds of body weight in the course of two or three days, an occasional patient has died with eclampsia. We then undertook a study of the control of cerebral irritability, using heavy sedation with Avertin and barbiturates. Even under profound and deep sedation, an occasional eclamptic patient dies. We next began a study of the control of hypertension. Patients with severe hypertension and rapidly recurring convulsive seizures were treated with antihypertensive agents and the blood pressure lowered to normal levels only in some cases to continue to convulse with blood pressures as low as 120/60. Some of these patients died with only moderate hypertension.

Invaluable, then, as these laboratory studies may be, they seem of doubtful clinical value. It is ironical that the communities which exhibit eclampsia cannot provide the facilities for its intensive study and when the communities can afford facilities for good clinical research, the economic and educational level of the people has improved to such an extent that the disease disappears. Perhaps we in Arkansas may have the good fortune to secure funds, personnel, and facilities to study this disease both in the laboratory and clinically.

The material which Dr. de Alvarez and his associates have presented gives us evidence that we can manipulate sodium and water stores, but having manipulated them in eclamptic women, I am not prepared to say that I have in any way altered the outcome of the disease.

DR. JOHN PARKS, Washington, D. C.—In their study of sodium metabolism the authors have presented preliminary results of sodium excretion as influenced by some fourteen therapeutic agents used in the toxemias of pregnancy. Because of Dr. de Alvarez's deep interest in the total subject of sodium metabolism, perhaps his future studies of sodium utilization, together with his current work on sodium retention and excretion, will indicate to us why the body tissues of pregnant patients and particularly of those who develop toxemia tend to retain an abundance of water and sodium.

For the clinician incompletely informed about the intricate and time-consuming methods of investigation used by the authors, thirty-six patients seems like a rather small series. However, a single journey through the renal tubules and delicate network of the glomeruli balancing water in one hand and sodium cations in the other is no simple trip. When urine output, renal plasma flow, glomerular filtration rate, sodium concentration in plasma, and the tubular rejection fraction of sodium and water are determined under controlled conditions

six times, then six times for each drug given, the complexity of this study becomes apparent. Technical interpretation of the results reported requires the talents of a renal physiologist.

In order to evaluate their effect it is important to know the method of administration of the five sedative drugs used. It has been our clinical impression that intravenous injection is the only controlled method of giving a sedative drug to an edematous patient. Medication administered hypodermically is absorbed slowly. Repeated doses of sedatives given subcutaneously or even intramuscularly seem to have a delayed and accumulative effect which becomes most profound when the patient begins to mobilize her extracellular fluids. The absorption factor of oral or rectal medication is even less reliable.

As one would anticipate, the results with plasma were rather indefinite. From our experience with systemic reactions, the hazards of plasma administration far exceed any potential benefits from its use in the toxemias of pregnancy. Since Dr. de Alvarez used both 50 per cent and 5 per cent glucose in his studies, perhaps he would give us his impressions of the comparative diuretic and therapeutic effects of these two different concentrations of glucose.

The pregnant patient presents an unparalleled opportunity for investigation of reversible hypertension. Our colleagues, the internists, are equally interested in these patients because knowledge of early and transitory hypertension offers a key to many medical problems. It is stimulating to see the methods of the biochemist and physiologist so ably applied to patients coming under the canopy of our specialty care as demonstrated by this and other papers presented at this meeting of the American Association.

DR. RICHARD BRYANT, Cincinnati, Ohio.—I think that Dr. de Alvarez mentioned at one point that the total period of time involved in a particular study was perhaps five hours. It seems legitimate to question the importance of a change which is recorded over only a five-hour period in a disease which not uncommonly extends over several weeks. An extension of the study might have changed the results. We know very definitely that in toxemia of pregnancy, even without treatment of any kind, the excretion of water, of sodium, and of other materials changes radically and apparently for no reason at all and in the excretion of water, there may be a spontaneous delay of 12 or 18 hours. I wonder, therefore, if five hours is a long enough period from which to draw valid conclusions. Sometime in the late nineteenth century we became imbued with the idea that every disease has a single cause for which there is a single treatment. I think possibly that toxemia of pregnancy is one of the diseases where that is not true, and in which a combination of medications should be used rather than a single medication. Although it is extremely valuable from the intellectual point of view to know the effect of each drug, I think it would also be valuable to know the effect of various combinations of drugs which have proved effective.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—Many studies of sodium in pregnancy have been reported and now potassium is the playboy for almost everyone with a flame spectrophotometer. I think sodium has something to do with toxemia of pregnancy, but just how, I do not know. Drs. Brown, Chesley, de Alvarez, and others have done excellent work on the renal excretion of sodium and other metabolites. However, we still do not know why edema occurs. We all thought that the sodium ion was in the extracellular fluids until ten years ago; that it was static, that is, it got there and stayed there. There have been sufficient experiments now with isotopes to show that the sodium ion is not static and that it is constantly shifting, but, for some unknown reason, in the pre-eclamptic patient it does not shift out of the body.

I think that there is very good evidence that the posterior pituitary and the adrenal cortex are in some way associated with the cause of pre-eclampsia and eclampsia. I cannot help but believe, however, that there is some other factor. What it is, I do not know. There is one other point that I would like to make. I think that the various reports very definitely indicate that many drugs are not the best drugs to use in the treatment of pre-eclampsia or eclampsia. I advise that you adhere to the time-tried drugs reported by competent investigators for the treatment of your patients.

DR. EDWARD C. HUGHES, Syracuse, N. Y.—The excretion and reabsorption of sodium and water depend upon the interplay between some of the hormones of the posterior lobe of the pituitary gland and the adrenal cortex. Some of the hormones of the posterior lobe in some species tend to cause the excretion of sodium and the retention of water, while certain hormones of the adrenal cortex produce retention of sodium and the excretion of water. Therefore, when this relationship is disturbed by any process, there may be altered retention and excretion of salt and water. This has not been completely worked out. I thought it would be interesting to report to you a preliminary study along these lines in respect to such relationship.

Studies on the excretion of the antidiuretic substance from the posterior lobe of the pituitary in normal pregnant individuals showed a slight increase as the pregnancy proceeded to term. We had thought that we would perhaps find a marked increase in the excretion of this material in the toxic patient, but this was not observed. There was, however, a slight increase. However, there was a definite, significant increase in a certain group of hormones in the toxic patient which resembled in their chemical formulas certain hormones of the adrenal cortex. This material resembled those hormones causing salt retention. We do not know whether such substance comes from the action of the adrenal cortex itself during these times, or whether it is an adrenal-like substance which may perhaps be excreted by the placenta.

This study, concerning the sedative and diuretic group of drugs used in toxemia which Dr. de Alvarez has presented to us today and which has been substantiated formerly by Dr. Brown, is in no way curative of the disease. The sedative group of drugs has an effect upon water and causes some control of cerebral irritation, whereas the diuretic drug tends to cause an elimination of sodium which, of course, is desirable. Therefore, we must continue to go forward and to seek further the cause of pre-eclampsia and eclampsia. The condition can be relieved by drugs, but the cure does not lie in them.

DR. DE ALVAREZ (Closing).—In reference to Dr. Bryant's question, I wish to make one point in particular. The results, as they are here tabulated in bar form, represent the actual determination of a five-hour period of study of each patient as well as representing the immediate effects of the drugs tested as they relate to the patient with pre-eclampsia. It was not our intention to indicate the latent effect of these agents, but to demonstrate the *immediate* response of pre-eclamptic patients to the various drugs when they are in the severest stage of the disease. For example, in a patient with severe toxemia of pregnancy with oliguria, we feel rather strongly, on the basis of our study, that Demerol is not the drug to use since it not only depresses the urinary output, but also increases reabsorption of sodium. In addition, even though we did not carry out our studies for an indefinite period of time, we did study each of these patients for a minimum of seventeen hours following the beginning of each study. In addition to the five hours required for the meticulous considerations from which our presentation today is made, the urinary output and total sodium excretion were followed hourly for the next twelve hours. Drs. Brown and Bradbury have shown in their studies that perhaps seventeen hours is not long enough, inasmuch as in one of their reports they studied the patients for several days, but not continuously. However, I should like to correct any impression that we are not aware of the fact that these patients are subject to a latent effect as well as from the drug used.

Dr. Bryant has also raised the question of the use of these test drugs in combination. We have done just that study, but do not have an adequate number of patients to give the over-all presentation that we should really like. We found that where a combination of drugs was given and adequate time allowed for the full effect to be demonstrated, the superimposition of an additional drug would provoke the effect of that single drug. To some patients we have administered as many as five different drugs, and have found that the drugs in any combination act exactly the same as they do when used independently.

I was especially intrigued by Dr. Dieckmann's statement regarding potassium metabolism. We, too, are guilty of paying particular attention to the sodium ion. In the past, sodium certainly has been the playboy in our investigation but with the advent of the flame

spectrophotometer we have found it possible to evaluate and study potassium. Because we felt it would merely confuse the issue and particularly because of the extensive ramifications involved in discussing sodium excretion, potassium excretion, and chloride excretion in the same presentation, we hope to bring before the profession the results of our study of the metabolism of these ions in forthcoming reports.

In reference to Dr. Parks' inquiry regarding the use of 50 per cent glucose, we have found that 50 per cent glucose produces practically no effect on water or sodium metabolism in pre-eclamptic patients studied by us. Tarail and his group at Yale have substantiated our impressions in working with medical patients with edema. They found that large quantities of hypertonic glucose failed to provoke appreciable depletion of augmented stores of water and salt. These observations also tend to confirm Dr. Dieckmann's statement that a good many of the drugs used in the management of pregnancy toxemia are of no real value.

I should like to clarify a point relative to the investigative methods used by us. In setting up and embarking upon our study, no attempt was made to reach any preconceived conclusions, since our research approach is designed to evaluate objectively, and without emotion, the results obtained.

ELECTIVE INDUCTION OF LABOR: IS IT JUSTIFIABLE IN NORMALLY PREGNANT WOMEN?*

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ONE of the important changes in attitude in obstetric practice is that concerning the elective induction of labor at term in normally pregnant women. The alleged increase in intrauterine fetal death and difficult labors in pregnancies which go past term is said to be prevented by this procedure which is rapidly becoming a commonplace method for managing pregnancy. In addition it is stated that the mother is freed from the concern as to when the baby will be born and whether or not she will arrive at the hospital in time for delivery.

Since the recorded series include the personal experience of skillful individual obstetricians or of well-controlled hospital groups, they do not represent the over-all outcome of elective inductions, many of which are performed without regard to all the details so important in reducing the danger. In spite of the excellent reported results it is necessary to examine the procedure not only from a point of view of technique and end result but as to its necessity. Any procedure which entails vaginal manipulation, rupture of the membranes, and the administration of pituitary extract, no matter how carefully it is carried out, increases the risk to the mother or the infant. Since it is as true now as it always has been that interference in normal pregnancy rarely is justifiable, we should continue to eliminate unnecessary procedures rather than to add potentially dangerous ones.

It is my impression that the mother and her child benefit less than does the physician by the unindicated induction of labor and that aside from his convenience little is accomplished by the procedure. In order to confirm this impression the following study was carried out.

Material

Over a four-year period 9,667 women were delivered in the obstetric division of the Temple University Hospital and of these labors 180 (1.86 per cent) were induced. For the purpose of this study only those patients who had had no obvious uterine contractions prior to artificial stimulation were considered. Those "induced" during the contractions of preliminary labor, those in early labor on admittance to the hospital with placenta previa or abruptio placentae, and those with spontaneous rupture of the membranes and irregular contractions to whom Pitocin was administered were omitted. The indications for the induction of labor in the group of 180 women are listed in Table I. It is obvious

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that in only the 27.8 per cent in whom labor was initiated electively was there no medical indication for the termination of pregnancy. Seven and eight-tenths per cent of these patients, however, had had rapid previous deliveries or lived at such a distance from the hospital that it was thought wise to control the labor and delivery. The remaining 36 inductions without definite indication were performed over the four-year period by eight different qualified obstetricians and on the supervised ward service. The greatest number of inductions by one individual during the period of this study was 17 and there were three who did only 1 each.

TABLE I. INDICATIONS

	WARD	PRIVATE	TOTAL	
Pregnancy toxemia	32	29	61	(33.9%)
Premature rupture of membranes	21	30	51	(28.3%)
Placental complications	8	9	17	(9.4%)
Recurrent pyelonephritis	1	0	1	(0.6%)
Elective—distance or short labor	1	13	14	(7.8%)
Convenience	3	33	36	(20%)
Total			180	

The causes of maternal morbidity for each indication are listed in Table II and those of fetal morbidity and mortality in Table III. It is of interest that the postpartum hemorrhage rate for induced labors, after those complicated by placental abnormalities are omitted, is slightly higher than the average rate for all patients. A larger group might well alter these figures.

TABLE II. MATERNAL MORBIDITY

	UTERINE INFECTION	FEBRILE ? CAUSE	URINARY INFECTION	HEMORRHAGE
Pregnancy toxemia (61)	7	0	3	2
Ruptured membranes (51)	4	2	3	0
Placental complications (17)	1	0	0	4 (2 hysterectomy)
Elective (50)	4	1	4	3
Pyelonephritis (1)	0	0	1	0

TABLE III. FETAL MORBIDITY, MORTALITY

	ASPHYXIA	INFECTION	STILL-BIRTH	DEATH	INJURY
Pregnancy toxemia	0	1	2	1	2*
Ruptured membranes	2	0	0	0	0
Placental complications	1	0	3	1	0
Elective	2	0	0	0	1†

*Cephalhematoma 1, fractured clavicle 1.
†Cephalhematoma 1.

If the elective induction of labor at term in normal women is important in the practice of obstetrics it should reduce maternal and fetal mortality and morbidity. In order to determine whether the mortality rates for either infants or mothers in this group of 9,667 deliveries might have been reduced by elective induction at term, all maternal deaths at that stage of pregnancy and all stillbirths and neonatal deaths in infants whose gestation periods had reached 40 weeks were studied. Since elective induction in normal patients is ordinarily considered only at term it does not seem likely that it would have been utilized in pregnancies not included in this study.

Results

Maternal Deaths.—There were no maternal deaths at this stage of pregnancy which might have been prevented by elective induction of labor.

In those pregnancies which by history had reached 40 weeks, 64 infants died; 24 were stillborn and 40 died during the neonatal period, usually during the first few hours after delivery.

Stillbirths (Table IV).—Of the 24 stillbirths, 14 were the result of obvious causes not preventable by induction of labor, hence only the 10 which occurred before or during labor and for which no cause could be determined need individual analysis. Of the 7 patients whose infants died before the onset of labor, 2 were delivered at the fortieth week of pregnancy and would not previously have been considered for induction. One infant died between 40 and 41 weeks, 2 between 40 and 42 weeks and 2 more between 42 and 44 weeks. Since no obvious causes for the deaths were determined, it is conceivable that earlier delivery might have permitted these 5 infants to survive.

TABLE IV. STILLBIRTHS, 40 WEEKS' GESTATION

Developmental anomalies	6	Death during labor	
Erythroblastosis	2	(No obvious cause)	3
Cord complications	4	Death before labor	
Injury at delivery	1	(No obvious cause)	7
Abruptio placentae	1		

In none of the 3 babies who died during labor would induction have altered the result. One died during normal labor at 40 weeks. In another there was a question as to whether the duration of pregnancy was 40 or 44 weeks; the infant who died during a normal labor weighed only 2,863 grams (6 pounds, 5 ounces). The third baby weighed 4,082 grams (9 pounds) and died during a labor complicated by primary inertia at 43 weeks' gestation. There was no question of disproportion and induction would not have prevented the abnormal mechanism.

Neonatal Deaths (Table V).—Of the neonatal deaths 24 must be discussed, since in only 16 was there an obvious cause not associated with the time of delivery.

TABLE V. NEONATAL DEATHS, 40 WEEKS' GESTATION

Congenital anomalies	11	Fetal distress during labor	7
Erythroblastosis	2	Breech delivery	4
Cord complications	2	Infection	4
Aspiration stomach contents	1	Injury	3
		Placenta previa	1
		Abruptio placentae	1
		Unknown cause	4

Fetal Distress During Labor (7 Deaths).—Six of the pregnancies were at the fortieth week of gestation and 1 was at 41 weeks. The largest infant weighed 3,543 grams (7 pounds, 13 ounces) and all were severely asphyxiated at birth and lived only short periods of time. The only abnormal labor was one complicated by primary inertia which was corrected early by intravenous dilute Pitocin solution; the fetal heart tones had been irregular before Pitocin was administered. There is no evidence to suggest that artificial induction would have prevented any of these deaths.

Breech Delivery (4 Deaths).—These deaths were all associated with the breech delivery rather than the failure to induce labor.

Infection (4 Deaths).—All 4 deaths occurred at the fortieth week of pregnancy and induction could not have prevented them. In one case, fetal death from pneumonia followed a long labor. Earlier termination of the prolonged second stage after progress had ceased might have altered the result. In another the membranes had ruptured spontaneously 8 days before the onset of labor and the infant died of pneumonia. The remaining 2 labors were normal in every respect; one infant died of pneumonia and the other of septicemia of unidentified origin.

Injury (3 Deaths).—All 3 of these deaths were from intracranial injury and occurred at the fortieth week of gestation. None could have been prevented by induction. The largest infant weighed 3,288 grams (7¼ pounds). In one the membranes ruptured spontaneously prior to the onset of labor which was normal. Another delivered precipitately after several hours of desultory contractions and the third labor was short and normal.

Placenta Previa (1 Death).—This patient was delivered by cesarean section because of a central placenta previa.

Abruptio Placentae (1 Death).—This patient had had a normal course until her admittance in labor at 40 weeks with evidence of placental separation and fetal distress.

Unknown Cause (4 Deaths).—Of the 4 who died of unknown causes one pregnancy was of 41 weeks' duration, the labor was normal, but the infant was asphyxiated at birth. One week previous to delivery the patient had been admitted to the hospital in false labor. Sterile vaginal examination at that time had revealed a long cervix with the presenting part at station –2, obviously not suitable for induction. Two others were at the fortieth week of gestation; one, a patient with severe rheumatic heart disease, was delivered after a normal labor of a healthy-appearing infant that died suddenly 24 hours later; the other, a patient with mild chronic hypertension, also had a normal labor but the baby died soon after birth. The fourth patient, 33 weeks pregnant by history, is included only because the infant who died with convulsions but without evidence of brain damage weighed 3,600 grams (7 pounds, 15 ounces).

From the analysis of fetal deaths occurring after the fortieth week of pregnancy there is little evidence to suggest that elective induction of labor could have altered the result. In only 5 pregnancies, all of which terminated in stillbirth, might elective induction at term have prevented fetal death. Even in these, however, there is no definite proof that the babies would have survived.

Comment

The reported results in elective induction of labor at term in normal women show a uniformly low fetal mortality which is to be expected since the fetal loss at this stage of pregnancy is at a minimum under any circumstance. It may appear that elective induction improves the result if, in an effort to establish the value of the procedure, the fetal loss in a series of normal term pregnancies terminated by elective induction is compared with total fetal mortality. In 2,697 deliveries in the Temple University Hospital during the past year the total fetal loss of infants weighing 1,000 grams or more at birth was 58 (21.7 per 1,000 live births); of these, 67 per cent weighed less than 2,500 grams, while only 20 per cent had reached the fortieth week of gestation. Coupled with this the fact that no more than 5 deaths in term infants during a four-year period in our hospital might conceivably have been prevented by induction of labor suggests that it seldom is necessary. Our problems with the postterm pregnancy and the postmature infant are virtually nonexistent and we are in complete accord with Calkins' opinion that true postmaturity is rare.

Approval by expert obstetricians, the supposed decrease in fetal mortality, and its convenience have led to the widespread use of induction by physicians unqualified either to perform it or to manage the complications which inevitably will arise. In such circumstances the morbidity and mortality must be high. Roblee noted a definite increase in maternal morbidity associated with induction of labor. The lowest rate occurred in elective inductions in normal pregnancy while the presence of a complication requiring termination increased it. Keettel, Diddle, and Plass in comparing 1,000 patients whose membranes had ruptured spontaneously with 1,000 in whom elective induction was performed by artifical puncture of the amniotic sac noted a substantial increase in intrapartum infection and prolapse of the cord and extremities in the latter group. If this occurs under carefully controlled conditions, what is the unreported mortality from the indiscriminate elective induction of labor by unskilled physicians?

Rather than to approve the routine induction of labor in normal women because it does not add substantially to the risk for mother or child, we should consider the practice in the light of whether or not it is necessary. If the end result of a large series of normal pregnancies in which labor is induced electively at term is better than that of a comparable group allowed to go into labor spontaneously, we should encourage it but if there is no improvement the practice should be abandoned. The gradual reduction in maternal mortality has been in a great measure due to the elimination of procedures which introduced infection or resulted in injury and hemorrhage. Induction of labor, particularly when carried out by unskilled physicians and in the face of contraindications, certainly increases the chance of infection and thereby the mortality for both mother and infant. The results of this study indicate that improvement in fetal and maternal mortality cannot be expected if all pregnancies are terminated at the calculated date of expected delivery.

The house staff and the medical students must be given a clear-cut conception of the indications for the induction of labor, the contraindications, the dangers involved, and the requirements which must be met before the operation can be considered. Careful, supervised, sterile vaginal examinations in the delivery room should be encouraged during the training period in order that they may become completely familar with the changes in the cervix preceding the onset of and during labor. Each patient for potential induction should be considered individually and a decision made as to whether or not her condition or her infant's will be improved by the interruption of the pregnancy. If termination is thought to be indicated sterile vaginal examination to determine the status of the cervix, the position of the infant, the station of the presenting part, and the adequacy of the pelvis must be carried out. Should any of these factors be unfavorable induction is contraindicated and another means of delivery must be selected. If these requirements are adhered to the incidence of induced labors will be low and most of them will be indicated.

Indications for Artificial Induction of Labor.—At the Temple University Hospital, these are:

Toxemia of pregnancy: The pregnancies of patients with pre-eclampsia, eclampsia, or hypertensive disease often must be terminated if medical therapy fails to halt the progress of the disease, or of those patients who have responded to treatment and in whom the condition is temporarily stabilized. The decision to delay induction in those cases of toxemia occurring several weeks before term may be followed by intrauterine death of the infant. Termination should be carried out after medical therapy has produced its optimum effect.

Premature spontaneous rupture of the membranes: If the membranes rupture the onset of labor is inevitable, but since the latent period is variable and since intrauterine infection and fetal death increase with prolonged rupture of the amniotic sac, early delivery is desirable. If the contractions have not

begun 12 hours after the membranes rupture, a sterile vaginal examination is performed to confirm the rupture and to determine the status of the cervix and the pregnancy. In those at least 37 weeks pregnant with a normal pelvis and a favorable fetal position and in whom the cervix is soft and effaced, an intravenous Pitocin drip is administered to initiate labor. Those whose cervices are unprepared are observed in the hospital and are treated prophylactically with aureomycin, terramycin, or with penicillin and a sulfonamide preparation.

Bleeding: Blood loss associated with placenta previa or premature separation of the normally implanted placenta may be sufficient to demand termination of the pregnancy. Ordinarily artificial rupture of the membranes alone is preferable for the minor degrees of placenta previa while a combination of this procedure and intravenous dilute Pitocin may be utilized for abruptio placentae.

Elective induction in the normally pregnant patient: If previous pregnancies have terminated precipitately, if the distance from the house of the patient to the hospital is great, or if reliable transportation is unavailable, elective induction may be considered. All of these indications apply primarily to the multipara and but rarely to the primigravida.

Miscellaneous: Occasionally induction is indicated for the patient whose previous pregnancies have terminated repeatedly in intrauterine death of the fetus. If no correctable cause can be determined, delivery before fetal demise may permit the birth of a normal infant. This occurs most often in association with chronic hypertension or metabolic diseases such as diabetes and nephritis. Certain infections such as pyelonephritis may be prolonged or made worse by the gestational changes in the urinary tract. If the infection persists or recurs despite adequate therapy, induction of labor may be considered.

Contraindications to the Artificial Induction of Labor.—These consist in general of the lack of indication. It is my opinion that the patient who enters the hospital for induction of labor and is subsequently discharged undelivered either because a medical induction fails or because conditions are not favorable for induction should not have been admitted originally. If one adheres strictly to indicated inductions those patients admitted and found unsuitable for the procedure should be delivered by some other means. However, in certain patients in whom there is adequate reason for the termination of pregnancy, induction is not always possible. Among the contraindications are (1) a long uneffaced cervix; (2) an abnormal pelvis making vaginal delivery doubtful; (3) abnormalities in fetal position and presentations; (4) a floating presenting part; (5) most cases of maternal cardiac disease, and (6) most patients in whom intrauterine fetal death has occurred.

Methods of Induction.—Artificial rupture of the membranes is the most effective means of initiating labor. If the cervix is adequately prepared, the vertex is presenting normally and is engaged and the pelvis is normal, amniotomy will shortly be followed by the onset of apparently normal labor. Dilute Pitocin solution may be administered intravenously if contractions do not begin within 12 hours after the membranes have been ruptured, for breech positions in which preservation of the membranes is desirable, or as an initial procedure if the fetal head is unengaged in a normal pelvis; in such an instance the membranes may be ruptured after descent has occurred.

Although it is recognized that in recent years the increased emphasis on prenatal care and other worth-while aspects of obstetric practice has increased the demand on the physician's time, elective induction of labor will not solve the problem. For the obstetrician with a relatively small practice, routine induction is unnecessary because it is unusual that all professional commitments

cannot be met. The physician who delivers more than 300 women a year, particularly if he also carries on a large office and gynecologic practice and works in a hospital inadequately supplied with residents, has difficulty in discharging his responsibilities to the patients under the best of circumstances, and induction, while it may relieve the problem somewhat, does not do so completely. An association with another obstetrician or a group will benefit both physician and patient, the former by the provision of time for study and leisure and the latter by the assurance that one of her own doctors will always be available either in the office or when she enters the hospital. Under such arrangements inductions for convenience are never necessary and the opportunities to supervise the patients more closely should improve the over-all results. The family physician may find it difficult to carry on an obstetric practice in conjunction with the rest of his work and as a result often resorts to unnecessary induction of labor. Since in many instances he has had little training in obstetric operative procedures and may not take time or know how to evaluate the patient for induction, the result may be disastrous. It is the responsibility of the obstetric staff of each hospital to set up and enforce rules concerning the induction of labor which should include not only the permissible reasons for the procedure but by whom and how it is to be done. A requirement for consultation with a qualified obstetric specialist who must evaluate the patient and record his findings, his decision, and the reason for the induction before it can be carried out should reduce the total incidence and particularly the number of inductions in cases in which contraindications are present.

There is no question but that the induction of labor can be done with relative safety on properly selected patients by properly qualified physicians but regardless of who performs the procedure an unavoidable risk is added for the mother and her infant. This risk is increased many times if all possible precautions are not taken. Since there is no proof that either fetal or maternal mortality is improved by induction of labor in normal pregnancy at term there is no justification for its use.

Discussion

DR. DANIEL G. MORTON, Los Angeles, Calif.—My only experience with the elective induction of labor by means of artificial rupture of the membranes, in any considerable number of patients, was obtained about twenty years ago. This was shortly after the time when Dr. Morris Slemons of Los Angeles reintroduced the method as a safe and effective one. We used it to induce labor in 150 patients, as an experiment to determine the limitations of the method. This experience taught us what ideal conditions were. It also taught us that the method was effective; we failed in only 2 patients who were later delivered safely. On the whole our results were entirely satisfactory. Since that time my experience has been confined to occasional cases in which I felt that there was a justifiable reason for inducing labor, along the lines to be discussed in a few moments.

I would like to consider first the philosophy involved in deciding upon the induction of labor. There are two principal viewpoints to be considered.

1. Induction of labor should be considered only when there is a definite abnormal condition present which threatens the life or health of mother or child should pregnancy continue. Actually, here, the indication is for termination of the pregnancy, and induction of labor is merely one of the methods of accomplishing it. Presumably, those holding this viewpoint feel that if induction of labor were indicated, efforts to accomplish it should be

pushed to the maximum and should they fail or be unwise another method of delivery should be chosen. This philosophy would exclude any tentative attempts at induction, even by medical means. The attitude is that *no* efforts at induction should be made unless one is so convinced of the necessity for terminating pregnancy, that one would be willing to push the decision to a conclusion and effect delivery one way or another.

2. The other line of thought envisages a sort of scaling of the indications for the induction of labor from very urgent to merely expedient, letting the degree of urgency govern the extent to which one will go to accomplish the induction. The methods we use to terminate a pregnancy are inextricably bound up with the urgency of the indications and the local conditions present in individual cases. This attitude is one which despairs of laying down hard and fast rules. As an example, if we are dealing with a fulminating pre-eclampsia which is getting worse, immediate action is desired. We choose either cesarean section or rupture of the membranes if local conditions are ideal. On the other hand, if we have under consideration a mild toxemia not getting worse, but present over an undesirably long period of time, the urgency for delivery is less, and it usually does not make much difference whether delivery is effected today or three days from now. Under these circumstances we might well try medical induction first, or we might rupture the membranes even if conditions are not ideal, realizing that some delay before actual delivery occurs is not of paramount importance. I favor the second viewpoint because it recognizes a scale of urgency and the necessity for correlating the method of induction with the degree of urgency, and the local conditions present in any given case.

Dr. Willson's paper deals with the less urgent circumstances and I think that he is right when he condemns elective induction of labor by means of rupture of the membranes in normally pregnant women at term, if he means *routine* induction of labor. Few of us would subscribe to such a routine even though we realize that with ideal conditions the risk is slight indeed. We would not do so because we know that complications can develop even under ideal circumstances, thus inviting unnecessary risk for mother and child. We know, too, how difficult it is to judge "term" and we know that the flesh is weak and that the temptation to go ahead with amniotomy, even when local conditions prove to be slightly less than ideal, cannot always be resisted. We know that such a procedure would set a bad example for others less skilled and less careful than ourselves, and we know that the responsibility is ours for whatever complication may appear, whether or not the induction procedures were actually responsible.

On the other hand, in my opinion, there *are* indications other than the usual medical ones which have been grouped under the heading of convenience, which might well be considered justifiable, provided there are no contraindications. They occupy a position at the lower end of the scale of urgency. They are considerations of expediency, rather than of pure convenience. Distant abode might come under this heading. Obviously, induction would not be indicated in all such cases, but for the multipara, definitely at term, with the vertex well in the pelvis, a normal position and pelvis and a flattened, gaping cervix, induction of labor by rupture of the membranes might well be sounder, more conservative obstetrics than standing by and letting come what will, whenever and wherever it will.

Increasing, excessive size of the fetus, difficult to judge though it is, might also fall into this category when local conditions are right.

I do not know whether there is such a thing as postmaturity or not, but I do know that one of my patients lost her baby because of death in utero, when I let her go more than a month beyond term as judged by what seemed to be a reliable menstrual history. The placenta showed an unusual amount of calcification. Today with the cervix ripe and other local conditions ideal, I believe that the induction of labor should be seriously considered when the patient has gone more than three weeks past her term.

I am even prepared to believe that the obstetrician's trip out of town, as for example to a meeting like this, may occasionally justify induction of labor. While none of us delude ourselves into thinking that our services are indispensable, some patients become so dependent upon us emotionally that our absence creates a situation which is definitely detrimental to

their well-being and may exceed the risk of the induction of labor under proper circumstances. I confess that I think this situation occurs rarely.

To go back to the title of the paper, "Elective Induction of Labor: Is it Justifiable in Normally Pregnant Women?" I believe with Dr. Willson that the only answer to this question is "No!" Pure convenience does not appear on our scale of urgency at all.

DR. MELVIN A. ROBLEE, Clayton, Mo.—Dr. Willson's paper is thought provoking and realistic. His advice should be followed. Essayists writing on induction of labor usually list only the references of kindred minds. Those for induction give one group of references and those against induction list another group. A clear over-all picture would be made if the opinion of both groups were combined.

Perhaps we might agree if only two indications for the induction of labor were considered: first, the obstetrical indication in the management of the toxic patient, including the patient with diabetes; second, the nonmedical indication with convenience and order as its only justification. When only convenience is at stake it is quite a risk to assume. Let us not make the mistake of subjecting the patient to a procedure because of the likelihood that the process will be successful. Rather, we should select the procedure of greatest safety and apply it to a particular patient.

In order safely to induce labor in a patient, we must have two conditions present: first, an anatomical change in the lower uterine segment and cervix and a physiological chemical change which would produce the spontaneous onset of labor within the next 48 to 72 hours. These observations are based on the study of patients in whom induction failed who later were either in spontaneous labor or became successful inductees. Also, combined maternal and fetal morbidity studies would show that babies of average or above average birth weight required a shorter than average labor and there was little or no morbidity noted. Whereas infants of less than average birth weights required a much longer labor and the morbidity factor was definitely increased. I would like to show a chart of 500 cases of spontaneous labors, not induced. You will see that labor occurred in most cases at a plus or minus 8 days of the estimated date of confinement with the highest average birth weight and the shortest hours of labor and again these cases showed the lowest morbidity, whereas the infants of less than average birth weight required longer hours of labor to be borr and these labors showed an increase in morbidity.

My chart bears out the contention of Dr. Willson that postmaturity rarely exists and certainly the estimated date of confinement alone is not sufficient evidence of maturity. It is true that the average birth weights of the babies were higher at some 16 days after the estimated date of confinement, but it is interesting to note that the birth weights were average at 25 days following the estimated date of confinement. This of course indicates a mistake in the calculation of the date.

From this we can conclude that the induction of labor confers no favorable influence. Therefore the induction of labor should be used rarely and cautiously, and only in patients requiring delivery some 48 hours in advance of the time that spontaneous labor would terminate their pregnancies. This acceleration would be of value in the management of the toxic patient and the diabetic patient, but would have little or no other obstetrical use.

DR. BAY JACOBS, Washington, D. C.—Dr. Willson has given an excellent presentation and his comments are of the type that one should make in a teaching capacity. In other words, in obstetric teaching the value of conservatism should be stressed. It is not often that one can improve upon nature.

A few years ago Dr. Roblee in a carefully prepared presentation attempted to show the ill effect of induction of labor as compared to results in large series of cases where pregnancy was allowed to terminate spontaneously. It was my impression at that time that there were no regulations limiting induction of labor in the hospitals from which his statistics were obtained and that the individuals involved knew very little about selection of cases or the conditions that must prevail before attempting induction. No doubt, similar circumstances may exist in any city.

At this point I should like to emphasize that the technique of induction is very simple and can be performed by anybody who is capable of doing a vaginal examination. However, it should not be done except by individuals who have acquired experience and good judgment. At times it is advisable to withhold induction even though the patient has been admitted to the hospital for that purpose.

Dr. Morton's discussion was somewhat confusing to me since he stated that occasionally he feels that induction of labor is justifiable for convenience, and then terminated with the comment that he agrees with Dr. Willson that it is never justifiable for convenience.

About two years ago Dr. Reycraft presented a large series of cases in which labor was induced. The results were excellent. Recently Hanley published his experience with amniotomy and his results also were good. Both these men induced labor in many cases for convenience, but they were very careful in their selection.

Dr. Willson reported that labor was induced in 1.86 per cent of his cases and if I understand him correctly these inductions were performed by good obstetricians whose experience in this respect was extremely limited, since each had induced labor in a very small number of cases over a period of four years. It is not fair to compare the experience of induction of these individuals with men like Reycraft and others who have demonstrated extensive experience and good results.

I was impressed by the final remark of our good and eminent friend, Dr. Fred Falls, two days ago when closing his discussion. He stated that one should not compare the merits of classical cesarean section and transperitoneal cesarean section when the one operation is usually done by a group of general practitioners and the other by a group of specialists. In like manner, I would like to say that one cannot discredit a valuable procedure like induction of labor and perhaps prohibit its use just because of unfavorable results obtained by inexperienced men. I agree that the procedure should be regulated and that only qualified individuals should be permitted to induce labor. Where hospital regulations are so stringent, as expressed by Dr. Willson, and induction except for strict medical indication is prohibited, a certain amount of resentment will arise among men of experience and good judgment. Personally I would prefer not to be a member of such a staff.

Although I believe in induction of labor for convenience in certain cases, I am not advocating its widespread unregulated use. A careful obstetrician will realize the responsibility that he assumes and will not subject his patient to any risk.

DR. JAMES REYCRAFT, Cleveland, Ohio.—In spite of this presentation, I have no reason to change my viewpoint expressed in my paper given two years ago. Since that time I have done approximately 200 elective inductions with perfectly good results. I think there is a tendency to confuse inductions for pathological conditions with those that are done for convenience, but I maintain that convenience is not for the doctor, but also for the patient. Many of our patients have requested that a repeat induction be done. We have done as many as three or four on the same patient because each time the necessary criteria were fulfilled. By that I mean that the presenting part was well engaged, the cervix was soft, it was ripe and dilated, sometimes as much as 6, 7, or 8 cm., and I think it would be absurd to let a patient in the latter condition go on and have the membranes rupture and have her baby in a taxicab when she could be delivered safely in a hospital under proper conditions.

The patient for induction comes in well prepared both psychologically and physically. She comes in after little or no breakfast and the induction is carried out, it is true at our convenience, but we try to suit it to her convenience as well. I still maintain that this procedure has a place in good obstetrics if done properly and carefully with due consideration for all the criteria involved.

Now there is a tendency, of course, to be overenthusiastic and perhaps induce labor in a case that is not suitable. If you stick close to your necessary criteria, I think it is a justified procedure.

I think Dr. Willson's paper is very good and, as Dr. Jacobs has said, from the standpoint of the professor and the teaching institution, you should be conservative. But there are

exceptions that a person learns through experience and this is a part, I would say, of the art of obstetrics that has a place in our field.

DR. WILLSON (Closing).—I should like to make my position on induction of labor perfectly clear. I am not attempting to make comparisons but simply to present our experience with a large group of patients in whom labor was not induced and to suggest that there is no real improvement in maternal and fetal mortality in the normal patient who is allowed to go into labor spontaneously.

The reference to "teaching" as contrasted to "nonteaching" hospitals concerns me a bit. I presume the meaning is university and nonuniversity hospitals. Every hospital should be a teaching institution and each individual who trains interns and residents has the tremendous responsibility of teaching proper conservative obstetric methods. I wonder if Dr. Jacobs is able during the few weeks an intern is assigned to his service to provide him with enough obstetric experience and judgment to allow him to induce labor safely. I am not concerned primarily with the inductions performed by the skilled, experienced specialist although I doubt that they are innocuous. I am concerned about the small general hospital in which the intern sees 50 to 75 per cent of labors induced and comes to believe that this is the normal and desirable method for every patient. I am concerned about practices such as I have been told are common in one community. The family doctor touches the membranes with a silver nitrate stick in his office and 24 to 48 hours later they rupture "spontaneously." I agree that the patient who lives a long distance from the hospital or the multipara with several centimeters of cervical dilatation is much better off delivered than at home, but I am certain that we should teach medical students, interns, residents, and family doctors that for the normal patient the spontaneous initiation of labor is preferable to induction.

HEPATIC FAILURE IN PREGNANCY*

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DURING pregnancy the liver seems particularly susceptible to damage by various noxious agents, and publications appearing early in this century suggested a definite association between hepatic necrosis and gestation. Cockayne,[1] in commenting on this phenomenon, theorized that the liver was "weakened" or somehow conditioned by pregnancy in a way which favored the development of massive necrosis of "acute yellow atrophy." On epidemiologic grounds, this author suggested that there was a relationship between infectious hepatitis and necrosis of the liver—a view substantiated more recently by Lucké[2] and others.

The virus of infectious hepatitis, of course, is but one of many agents which may cause severe liver injury.[3, 4, 5] It is well known that liver damage, presumably on a vascular basis, may occur in pregnancy complicated by acute toxemia.[6, 7] Abundant clinical and experimental data accumulated during the past two decades have also shown that hepatic injury may result from nutritional deficiencies.[8, 9]

Although it is not the purpose of this report to consider in detail the nutritional aspect of pregnancy, it is apparent from many studies that the requirements for certain nutrients are increased during gestation, and some data[10] suggest that complications of pregnancy seem to be associated with dietary deficiencies. The concept of Himsworth and his co-workers, that trophopathic and toxopathic factors are involved in the production of liver injury, seems pertinent in this connection; it seems likely that the trophopathic or nutritional factor conditions the liver for injury by a chemical or infectious agent.[13]

That the problem of liver injury in pregnancy has clinical significance is indicated by the findings of the North Carolina Committee on Maternal Welfare in its review of 1,200 maternal deaths. Probable hepatic failure was diagnosed clinically or by autopsy as a cause of death in 21 (1.7 per cent) of these cases. The present study is based on a review of these 21 cases, and on the records of 2 patients, observed by us, who survived the development of hepatic injury in association with toxemia of pregnancy.

Clinical Material and Observations

The records of the North Carolina Maternal Welfare Committee are obtained by questionnaires sent to the physicians reporting maternal deaths. The

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TABLE I. SUMMARY OF CLINICAL AND ANATOMIC FINDINGS IN GROUP A (NINE FATAL CASES OF PRIMARY HEPATIC INJURY DURING PREGNANCY)

CASE NO.	RACE	AGE (YR.)	PREVIOUS PREGNANCIES	DURATION OF PREGNANCY (WEEKS)	INITIAL SYMPTOMS	OUTCOME OF PREGNANCY	DURATION OF SYMPTOMS BEFORE DEATH	COURSE OF DISEASE	ANATOMIC FINDINGS
1	W (NCMW 816)	19	0	20	Case history given in body of article				Massive hepatic necrosis
2	W (NCMW 544)	27	0	40	Case history given in body of article				Same as Case 1
3	W (NCMW 394)	24	0	40	Case history given in body of article				Same as Case 1
4	C (NCMW 144)	32	8	40	Epigastric pain	Spontaneous delivery	4 days	Progressive jaundice, coma	No autopsy
5	C (NCMW 450)	41	5	40	Headache, lassitude	Spontaneous delivery	9 days	Progressive jaundice	No autopsy
6	W (NCMW 722)	34	5	40	Malaise, fourteenth postpartum day	Spontaneous delivery, live infant	12 days	Progressive jaundice	No autopsy
7	C	35	0	12	Jaundice following abortion	Abortion	14 days	Progressive jaundice, coma	No autopsy
8	W (NCMW 795)	32	2	34	Nausea, epigastric pain, headache	Amniorrhexis, live infant	10 days	Shock, progressive jaundice	No autopsy
9	W (NCMW 318)	20	0	40	Epigastric pain, nausea, vomiting	Spontaneous delivery, live infant	3 days	Progressive jaundice	No autopsy

amount of clinical and laboratory data recorded is directly related to the ability and cooperation of the physician and to the clinical facilities which are available to him. Although we have limited information concerning some of the cases, none were included in this report unless the clinical or anatomic record indicated significant liver damage. All of the 23 patients in this series had progressive jaundice associated with a course indicative of liver disease, or evidence of significant hepatic injury at autopsy. Autopsies were performed by a qualified pathologist in 12 cases. One of these (Case 1) was from the obstetric service at the North Carolina Baptist Hospital.

The clinical records of the 23 patients and the autopsy findings in 12 cases are summarized briefly in Tables I and II. The cases have been divided into two major groups. Included in Group A are the 9 patients whose terminal illness was apparently due to primary hepatic failure. Group B is made up of 14 patients who had acute toxemia of pregnancy with evidence of significant damage to the liver.

Group A.—

The 9 patients in this group were entirely well until the acute onset of the terminal illness. Although epigastric pain, nausea and vomiting were the most frequent presenting complaints, some patients had vague, nonspecific symptoms. A low-grade fever was present in 7 cases. Albuminuria, hypertension, or both appeared irregularly. All the patients had jaundice, and in all cases the course of the disease was rapidly progressive. Stupor, mental confusion, coma, and death ensued within three to sixteen days after the first evidence of illness.

Age, race, and parity are apparently not significant factors in this group. Seven patients were in the third trimester of pregnancy, and 6 of these were at term. Abortion or delivery occurred spontaneously in all cases, except for one in which labor was induced by amniorrhexis. Five living children were delivered. One patient had been treated for syphilis with arsenic and bismuth four years prior to death. No other history of a toxic agent or antecedent liver injury was obtained. None of the cases are known to have occurred in association with epidemic viral hepatitis.

Massive hepatic necrosis was found in the 3 cases in which autopsies were performed. The clinical course of the other 6 cases was typical of this condition. Although methods of treatment varied widely, the course of the disease was apparently not altered by any of them.

Group B.—

The 14 patients in this group all had evidence of extensive hepatic injury associated with severe toxemia of pregnancy. This group includes our two nonfatal cases. Jaundice was a prominent clinical feature of the disease in 8 cases, including the 5 which did not come to autopsy. Clinical evidence of shock was sometimes observed: 7 patients had severe hypotension. In the 12 fatal cases the acute terminal phase of the illness lasted from one to ten days. Seven deaths were fulminant, occurring in seven to forty-eight hours after the onset of acute symptoms. The fulminating course of the illness and the appearance of jaundice are at variance with the usual clinical picture of severe toxemia of pregnancy.

As in Group A, age, race, and parity do not seem to be significant factors with reference to hepatic involvement. In 13 cases the type of toxemia was classified. Four had hypertensive cardiovascular disease with superimposed toxemia, one progressing to eclampsia. Nine had pre-eclampsia which in 4 cases progressed to convulsions and coma. Hypertension, albuminuria, and edema were present in all cases, and autopsy studies performed on 9 patients showed varying degrees of hepatic necrosis and hemorrhage consistent with eclampsia.

TABLE II. SUMMARY OF CLINICAL AND ANATOMIC FINDINGS IN GROUP B
(FOURTEEN CASES OF HEPATIC INJURY ASSOCIATED WITH TOXEMIA OF PREGNANCY)

CASE NO.	RACE	AGE (YR.)	PREVIOUS PREGNANCIES	DURATION OF PREGNANCY (WEEKS)	OUTSTANDING CLINICAL FEATURES		OUTCOME OF PREGNANCY	TREATMENT RESULTS	DAY OF DEATH (AFTER ADMISSION)	ANATOMIC FINDINGS
					BEFORE DELIV.	AFTER DELIV.				
10	W (NCMW 948)	45	11	39	Toxemia, edema, albuminuria BP 220/120	Shock without hemorrhage	Spontaneous stillbirth		Second	Focal and diffuse necrosis
11	C (NCMW 983)	38	0	23	Jaundice, convulsions, coma. Edema, albuminuria BP 240/140		Undelivered		Third	No autopsy
12	W (NCMW 593)	26	0	32	Toxemia, epigastric pain. Edema, albuminuria BP 180/120		Undelivered	$MgSO_4$ shock, jaundice	Fifth	Focal necrosis
13	W (NCMW 360)	40	4	38	Abdominal pain (RUQ), toxemia, jaundice, edema, albuminuria BP 170/100		Postmortem stillbirth		Sixth	No autopsy
14	W (NCMW 691)	39	2	30	Toxemia, stupor, edema, albuminuria BP 190/130		Undelivered		Second	Focal necrosis
15	C (NCMW 710)	26	2	30	Toxemia, abdominal pain, convulsions, coma. Edema, albuminuria BP 180/130		Undelivered		Fourth	Focal necrosis
16	W (NCMW 17)	27	2	30	Toxemia, premature sep. of placenta. Edema, albuminuria BP 180/130	Epigastric pain, jaundice	Spontaneous stillbirth		Eleventh	No autopsy
17	C (NCMW 817)	23	-	-	Toxemia, premature sep. of placenta. Edema, albuminuria		Undelivered		Third	Focal necrosis
18	C (NCMW 1096)	39	11	40	Chronic HCVD, toxemia, congestive failure BP 180/120		Undelivered		Third	Diffuse focal necrosis and hemorrhage

19	W (NCMW	27 1032)	2	30	Nausea, vomiting, premature sep. of placenta	Hemorrhage, jaundice, coma, convulsion	Spontaneous stillbirth	Transfusion reaction	Sixth		Focal necrosis, extensive
20	W (NCMW	24 842)	0	40	Toxemia, convulsion. Edema, albuminuria BP 210/120	Shock without hemorrhage, coma	Outlet forceps		First		Focal necrosis
21	W (NCMW	30 119)	0	40	Toxemia, nausea, vomiting, convulsion. Edema, albuminuria BP 198/120		Postmortem delivery	Veratrum; coma, cerebral hemorrhage	Second		Focal necrosis and hemorrhage
22	W (NCBH	24 101878)	0	34	Toxemia, epigastric pain, dark urine, jaundice. Edema, albuminuria BP 180/110	Shock	Spontaneous delivery, live infant	Methionine, glucose, transfusion	Recovered		
23	W (NCBH	17 146304)	0	40	Nausea, toxemia, albuminuria, edema. BP 190/100	Stupor, jaundice	Spontaneous delivery, live infant	Methionine, glucose	Recovered		

In Table II the term "focal necrosis" is used to designate these pathologic changes, but it should be noted that extensive destruction of the entire liver was found in 5 of the 9 patients.

Report of Cases

These cases are selected because more information is available for them than for the others. The first 3 cases reported are from Group A; the fourth is from Group B.

CASE 1.—(NCMW 816.) This patient was a 19-year-old white primigravida who was transferred to the North Carolina Baptist Hospital for the diagnosis and treatment of coma on Jan. 17, 1950, at 20 weeks' gestation. Her prenatal course had apparently been normal until January 12, five days prior to admission, when she noted for the first time the onset of mild epigastric pain. This pain was progressive in severity and became associated with nausea and vomiting on January 14. On January 16 the onset of stupor was noted; this progressed rapidly to coma from which the patient could not be roused.

The past history was significant in that the patient had received antisyphilitic therapy, presumably bismuth and arsenic, in 1946 because of the finding of positive serologic tests for syphilis. In addition, a course of penicillin therapy had been given in September, 1949, after the diagnosis of pregnancy was established. For a number of years the patient had subsisted on a diet poor in protein, rarely eating meat or eggs, and only occasionally consuming small amounts of milk. No history of exposure to industrial chemicals or of recent drug usage was obtained.

Physical examination on admission showed the temperature to be 100° F., the pulse 100, the blood pressure 150 systolic, 60 diastolic. The patient was comatose, responding only slightly to painful stimuli. The skin and sclera had an icteric tint. The eyes were fixed; the pupils were equal but dilated, reacting well to light. Examination of the heart and lungs showed no significant abnormality other than sinus tachycardia. The uterus was gravid, measuring 18 cm. above the symphysis. No fetal heart sounds were heard. The area of hepatic dullness was definitely decreased. Deep tendon reflexes were equal but somewhat hyperactive; no pathologic reflexes were elicited. There was no edema present.

Laboratory studies showed a hemoglobin of 13 Gm. per 100 c.c., 5.1 million red blood cells and 17,200 white blood cells per cubic millimeter, with 71 per cent polymorphonuclears. The urine was dark and contained 20 to 30 white blood cells per high-power field; no albumin or sugar was detected although acetone (4 plus) and bile were present. The nonprotein nitrogen was 46 mg. per 100 c.c., serum chlorides 124 meq. per liter, serum cholesterol 195 mg. per 100 c.c., serum proteins 5.4 Gm. per 100 c.c., blood sugar 100 mg. per 100 c.c. The carbon dioxide combining power was 14 meq. per liter. The icterus index was 42 units, alkaline phosphatase 8.1 Bodansky units. The Kahn and Wassermann reactions were both positive. The prothrombin time was markedly prolonged, no clot being obtained in 2.5 minutes (control, 14 seconds).

Parenteral fluids, including liberal amounts of glucose, methionine, vitamins, and sodium lactate, were administered without apparent effect. Shortly after admission several generalized convulsions occurred, and the patient vomited dark blood intermittently. Approximately 16 hours after admission spontaneous abortion occurred, associated with moderate bleeding which responded to oxytocic agents. The patient died one hour later without having roused from her coma.

The pathologist's report on the postmortem examination of the liver was as follows:

Gross Findings.—The liver was small and flabby, weighing 600 grams. The capsule was smooth and glistening. The surface was dark reddish brown with punctate brighter red areas. The kidneys were slightly enlarged and softened with ecchymoses in the cortex. There were also ecchymoses of the myocardium, lungs, small intestines, diaphragm, and renal pelves.

Pathologic Histology.—The structure of the liver in this instance was one of complete loss of hepatic cells. There was not one cell evident which appeared intact except those associated with small bile ducts, the proliferation of which was apparently just beginning.

Marked congestion was found throughout the liver, and in some instances there appeared to have been a wide breakdown of the sinusoidal endothelium with permeation of the parenchymal spaces by erythrocytes. Numerous phagocytes remained in the liver without particular arrangement, and pigment was prominent in these cells. A moderate lymphocytic infiltration was found around the bile ducts in what represented the portal spaces. In some areas, there was a more recent involvement with an occasional remaining parenchymal cell in the advanced stages of degeneration. In a few areas hepatic lobules remained, but these were necrotic and removal of debris had not been completed. Other areas showed a more marked inflammatory reaction around necrotic lobules, with sinusoids loaded with mononuclear phagocytes. The predominant method of clearing the necrotic cells, however, was certainly not one of phagocytosis but of liquefaction and complete dissolution. Trichrome stains showed no increase in fibrous tissue.

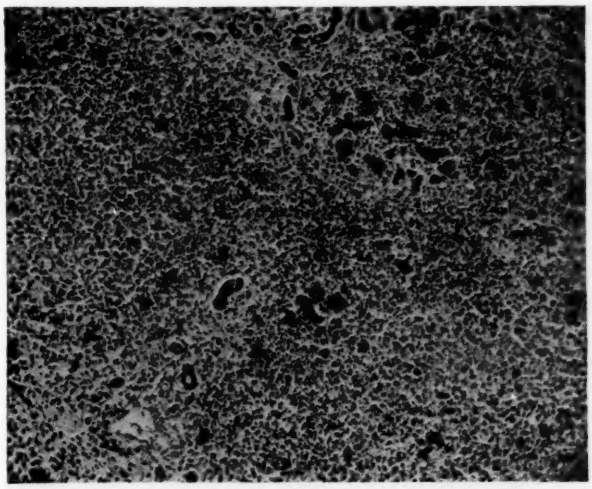

Fig. 1.—Representative section of liver from Case 1. Note the extensive necrosis with complete loss of normal arrangement.

CASE 2.—(NCMW 544) A 27-year-old white primigravida in active labor was hospitalized at term on Aug. 29, 1948. Until August 22, when she began vomiting at night, her prenatal course had been normal except for obesity and a total weight gain of approximately 34 pounds. On August 24, the blood pressure was recorded as 120 systolic, 90 diastolic; moderate pitting edema of the feet and ankles was demonstrated, and a voided specimen of urine was found to contain a slight trace of albumin. A diagnosis of multiple pregnancy was established by roentgen examination. On several occasions during the week prior to admission the patient had complained of "blind spells" during which she was unable to read or distinguish faces.

Physicial examination on admission showed icterus of the skin and sclera. Massive edema of the lower extremities was present and extended to the level of the umbilicus. Sacral edema was evident. The blood pressure was recorded as 136 systolic, 80 diastolic. The patient was confused and irrational. She was unable to void, but a few cubic centimeters of dark brownish urine was obtained by catheterization. Analysis of this specimen showed albumin (3 plus), together with granular casts, erythrocytes, and white cells. Subsequent urine specimens gave a 3 to 4 plus reaction for albumin.

After fifteen hours of labor the patient was delivered under local anesthesia of stillborn macerated twins. Her immediate postpartum condition was poor. The blood pressure fell to 70 systolic, 50 diastolic, and there was moderately severe postpartum bleeding although the uterus contracted well. She was given a transfusion of 500 c.c. of whole blood, together with 500 c.c. of saline and 1,000 c.c. of glucose. Bleeding was apparently controlled by

oxytocics. She was maintained with daily infusions of 1,000 c.c. of 25 per cent glucose in water to which methionine and vitamins were added. Penicillin was started post partum.

On the first postpartum day the total output of urine was 40 c.c. Marked abdominal distention developed but was relieved by the use of Wangensteen's suction apparatus. On the second postpartum day the total urinary output was 65 c.c., and on the third postpartum day (September 1) 60 c.c. For two days following delivery the patient's sensorium remained clear, but she lapsed into coma on September 1 and died on September 3, the fifth postpartum day.

Laboratory Data.—On August 29 the nonprotein nitrogen was 74.5 mg. per 100 c.c.; the serum bilirubin was less than 0.3 mg. per 100 c.c. The icterus index was 22.2, coagulation time 3 minutes and 20 seconds. On August 30 the serum proteins were 5.1 Gm. per 100 c.c., the albumin-globulin ratio 2.4:2.7. The van den Bergh reaction was immediate and direct, showing 15.7 mg. of bilirubin per 100 c.c. The icterus index was 100; the hemoglobin 66 per cent. On September 1 the nonprotein nitrogen was 126 mg. per 100 c.c.; the white blood cell count 58,000. On September 2 a Kahn test was negative, and the white cell count was 57,400.

The pathologist reported the following changes in the liver:

Gross Findings.—The liver was apparently normal in size and the capsule smooth and glistening. Externally the organ exhibited a light tannish-yellow color. The inferior margin was sharp. On section the tissue was rather firm in consistency and tannish yellow in color, with the architecture moderately obscured.

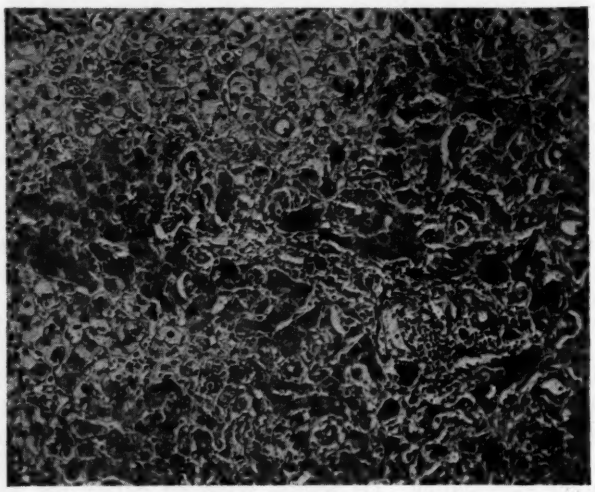

Fig. 2.—Representative section of liver from Case 2, showing distortion of architecture, with swelling, vacuolization, and necrosis of cells located predominantly in the central portions of the lobules. Proliferation of small bile ducts is seen in the lower right of the photograph.

Pathologic Histology.—The changes in this liver were entirely different in structure from those noted in the previous case. Here there was some destruction of lobular architecture, but the predominant change appeared to be a central necrosis of the hepatic cells. This necrotic change was not one of complete dissolution of the cells but more a dissolution of cytoplasm with persistence of pyknotic nuclei and cellular outlines. The zones appeared as pale foci in an otherwise well-stained background. The necrotic areas showed further change with dropping out of nuclei and loss of cell membranes, apparently representing a further-advanced stage of the lesion.

In some areas, in the larger foci, inflammatory cells were noted within the sinusoids; some of these consisted mainly of lymphocytes with a few polymorphonuclear leukocytes and with mononuclear phagocytes. Other cells in the involved lobules were somewhat swollen, and

in many the architecture of the cords was disrupted. The arrangement in these areas was one of loss of orientation and lack of hepatic sinusoids between cells in which no cordlike configuration was found. Lipid retention was apparent in a few of the cells which apparently were more intact, but fatty metamorphosis was not a prominent feature.

Lymphocytic infiltration in the portal spaces was prominent, with a moderate number of larger mononuclear cells and an occasional neutrophilic leukocyte. Slight proliferative change was noted in the bile canaliculi. There was no bile retention in the smaller ducts.

Here and there throughout the liver, particularly at the edges of the lobules, one gained the impression that fibroblastic activity was taking place with a few proliferative, elongated cells located between the vessels and bile ducts. Such a change was not found in the lobules themselves. There was much pigment found in phagocytes within the sinusoids in those areas showing early necrosis.

CASE 3.—(NCMW 394) A 24-year-old white primigravida at approximately 40 weeks of gestation was admitted to a hospital on Feb. 28, 1949, because of jaundice. The prenatal course had been uneventful until about one week before admission when she had noted "indigestion," characterized by occasional nausea and vomiting, together with progressive pain and tenderness in the right upper quadrant. On February 25, jaundice developed.

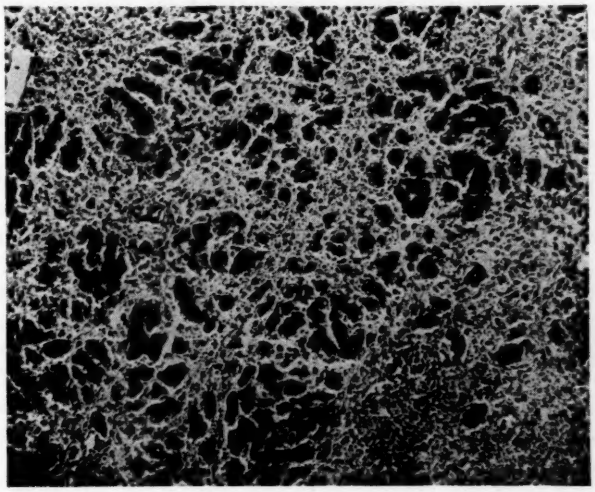

Fig. 3.—Section of liver from Case 3 to show the extensive necrosis and loss of parenchyma. Many of the remaining cells in this photograph are pyknotic.

Examination showed a moderately obese white woman with definite icterus of the skin and sclera. The temperature and pulse were normal and the heart and lungs showed no abnormality. The blood pressure was recorded as 115 systolic, 80 diastolic. The spleen and liver were not palpable. Very little tenderness could be elicited over the liver. Examination of the extremities was negative.

A urinalysis showed traces of albumin and sugar and examination of the blood was within normal limits.

The patient was placed on a high carbohydrate diet, and except for occasional vomiting her hospital course was uneventful until March 3. At that time labor began spontaneously, and after 24 hours a normal male infant weighing 6 pounds, 14 ounces, was delivered by low forceps under ether anesthesia administered by the drop method. The third stage of labor was not abnormal.

Approximately ten hours following delivery the patient's condition suddenly became worse. The jaundice deepened, the pulse became weak, and respirations were shallow and irregular. She perspired profusely and the skin was cold. Some vaginal bleeding was noted

but was not considered excessive. The blood pressure was 110 systolic, 70 diastolic. The patient became progressively stuporous. She was given copious amounts of glucose intravenously and was placed in an oxygen tent. On the second postpartum day the stupor progressed to coma, and pulmonary edema developed. The patient's condition continued to deteriorate and she died on the third postpartum day, March 7, 1948.

Laboratory Data.—On February 29 the urine was light amber with an acid reaction, a specific gravity of 1.009, and a trace of albumin and sugar; microscopic examination was negative. The icterus index was 22; the van den Bergh reaction was direct and showed 2.8 mg. of bilirubin per 100 c.c. On March 1 the white cell count was 10,150 with a normal differential; the red cell count was 3,820,000; the hemoglobin 83 per cent. On March 3 the icterus index was 105, the prothrombin time 22 seconds (control, 14 seconds). On March 5 the fasting blood sugar was 33.3 mg. per 100 c.c. On March 6 the fasting blood sugar was 25 mg. per 100 c.c. The urine was positive for bile, negative for sugar, had a 1 plus reaction for albumin and contained numerous cellular casts. A blood count showed 31,400 white blood cells, with 72 per cent polymorphonuclear leukocytes.

Pathologic examination of the liver revealed the following changes:

Gross Findings.—The liver was reduced in size, weighing approximately 1 kilogram. The surface was smooth with mottled reddish areas and the consistency was normal.

Pathologic Histology.—Examination of sections of the liver showed a diffuse necrosis of hepatic cells which involved all the tissue examined. It appeared that necrosis had primarily occurred in the peripheral and central zones more or less simultaneously, but this change was not limited to those areas, and usually involved the entire hepatic lobules. In areas in which the hepatic cells had disappeared, the stroma had collapsed and sinusoids were outlined by the presence of red blood cells only. In some instances the sinusoidal lining had ruptured, allowing an extravasation of red cells into the empty hepatic cords.

The inflammatory reaction in this liver appeared to be limited to those areas immediately surrounding the small bile ducts, in what apparently represented portal spaces. There was no inflammatory reaction except for a few isolated foci of lymphocytes scattered here and there throughout the liver with an occasional phagocyte which was still present in the sinusoids. Proliferation of the small bile ducts was found, but was not a prominent feature. Bile thrombi were present in some of these canaliculi. In the liver cells themselves, no definite lipid retention was found, though many of them showed evidence of swelling and some dissolution of cytoplasm and loss of nuclear detail. In a few foci, giant liver cells were noted with large nuclei suggestive of regeneration.

CASE 10.—(NCMW 948) A 45-year-old white woman in her twelfth pregnancy was admitted to a hospital on Sept. 5, 1950, in early active labor at 39 weeks of gestation. Two weeks prior to admission the patient was found to have severe hypertension with a blood pressure of 220 systolic, 120 diastolic, moderate edema of the hands and feet, and albuminuria (2 plus). Hospitalization was advised at that time but refused by the patient.

On admission the systolic pressure varied from 270 to 300 systolic with a diastolic pressure of 130. Mild pitting edema of the legs was present, and analysis of the urine showed a 4 plus reaction for albumin and many granular casts. The fetal heart rate was 136 per minute. The patient was given hypertonic glucose, Demerol, and sodium phenobarbital without apparent response. She was considered to be in "good condition," however, when admitted.

The past history was significant in that severe hypertension had complicated two previous pregnancies.

On September 6 a stillborn infant was delivered spontaneously under nitrous oxide and oxygen anesthesia. The blood pressure immediately prior to delivery was 210 systolic, 150 diastolic. No excessive bleeding attended the third stage of labor. Following delivery the patient's condition was poor. She exhibited signs of shock, and gradually became comatose. Signs of acute congestive heart failure developed which showed no apparent response to digitalization. The patient died on September 7.

The pathologist reported the following changes in the liver:

Gross Findings.—The liver weighed 1,900 grams. The capsule was smooth and externally numerous areas of purplish discoloration could be seen beneath the capsule. These areas were softened, 2 to 3 cm. in diameter, and on cut section showed hemorrhage and loss of liver structure. Approximately 60 per cent of the liver substance was represented by these areas.

Pathologic Histology.—Sections of the liver showed a moderate degree of fatty metamorphosis, particularly noted in the peripheral cells of the lobules. In those areas which were better preserved, foci of central necrosis were present. There were also foci in which complete necrosis of the parenchymal cells was found, with disruption of architecture and with disappearance of the parenchyma. These areas involved numerous lobules and alternated with areas of more normal architecture. An occasional group of necrotic lobules was present within an otherwise nonnecrotic area of tissue, while here and there one found areas of apparently fairly well-preserved tissue within a necrotic focus. The character of the necrotic change in these areas of the liver was one in which there was coagulative necrosis, with preservation of the cellular outlines but with nuclei in advanced stages of necrobiosis. The nuclear outlines were usually indistinct and often had disappeared. The rest of these areas, as well as portions of the areas themselves, were infiltrated by neutrophilic leukocytes with a few mononuclear phagocytes. Pigment-containing phagocytes filled many of the sinusoids which remained in the necrotic areas, but were absent in the better-preserved section.

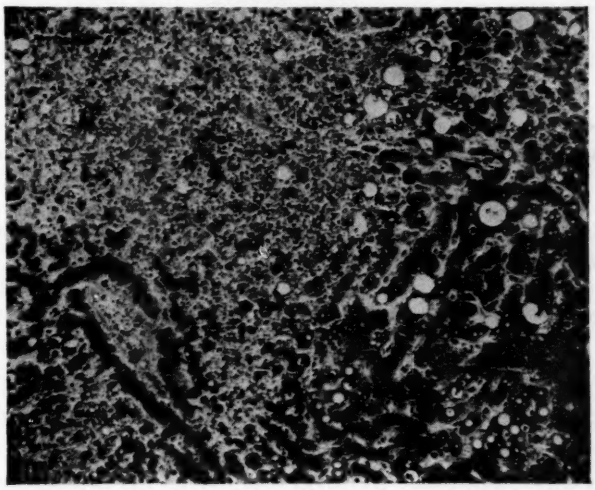

Fig. 4.—Representative section of the liver showing one of the areas of coagulative necrosis bordered by better-preserved cells. The latter are in the earlier stages of necrosis with cytoplasmic swelling, pyknosis, and fatty change.

Comment

The Importance of Hepatic Failure as a Cause of Maternal Deaths.—We believe that any clinical or laboratory evidence suggesting that liver injury may be developing in association with pregnancy must be regarded with concern. Although the reported incidence of acute hepatic necrosis complicating pregnancy ranges from one case in 5,000 deliveries[11] to less than one in 20,000,[12] liver failure may well be a contributing factor in maternal deaths which are attributed to a wide variety of conditions. As has been previously noted, severe liver involvement was diagnosed on clinical grounds in 1.7 per cent of the first 1,200 maternal deaths reviewed by the North Carolina Committee on Maternal Welfare. It is impossible to assay the precise role played by hepatic failure in these cases, particularly in the absence of necropsy studies.

Nevertheless, this high incidence of clinically apparent liver disease in pregnancy suggests that the importance of hepatic failure as a direct or contributory cause in maternal deaths may not have been adequately recognized.

Factors Contributing to Hepatic Injury During Pregnancy.—

An interesting point for speculation is the possible basis for the association of acute hepatic necrosis with gestation. The various factors which may contribute to the pathogenesis of this condition are shown in Fig. 5. Most authors are in agreement that pregnancy seems to favor the development of massive hepatic necrosis,[1, 12, 13] but significant statistics concerning the actual incidence of this condition in pregnant women are difficult to obtain because of its relative rarity.

Himsworth[9] believes that the higher incidence of "acute yellow atrophy" of the liver during pregnancy is related to nutritional factors.[13] It is entirely conceivable that the various agents, microbial or chemical, which are known to cause liver damage meet less resistance in a liver that has been "conditioned" by suboptimum nutrition. Zondek's[14] observations on "acute yellow atrophy" occurring during pregnancy as a complication of infectious hepatitis lend support to this thesis. The majority of patients that he observed were obviously undernourished.

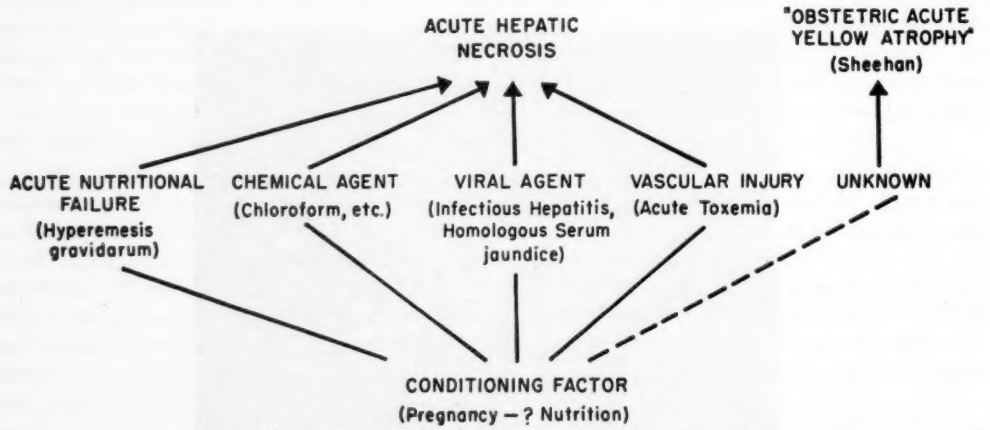

Fig. 5.—Diagram showing the relationship between various etiological factors in hepatic necrosis.

With particular reference to viral hepatitis in pregnancy, the relatively benign course of this disease in certain series[16, 17, 18] may be accounted for by strains of low virulence which have been noted in some epidemics,[15] or by the absence of a nutritional conditioning factor. Undoubtedly both the virulence of the viral agents and the susceptibility of the liver to injury may vary considerably. Since these factors are impossible to assay in the individual patient, any evidence of hepatic disease complicating pregnancy must be considered as potentially very hazardous.

The possible interrelationship of inadequate nutrition, acute toxemia, and liver injury is of more than theoretical interest. Although a direct etiological relationship between poor nutrition, particularly protein deficiency, and acute toxemia of pregnancy is difficult to establish, there are many reports in the literature suggesting such an association.[10, 19-23] Conceivably, defective nutrition may not only play a part in the development of toxemia of pregnancy, but may at the same time make the liver more susceptible to injury arising on a vascular basis as a result of the toxemia (Fig. 5). Although clinical and experimental evidence in direct support of this view is lacking, we feel that the possibility

of such synergism is definite enough to emphasize further the importance of adequate nutrition in pregnancy. We believe that whenever hepatic disease is suspected, it is imperative that the patient be supplied with an adequate diet, orally or parenterally. The time-honored administration of glucose alone affords inadequate "protection" for a liver damaged by chronic protein depletion or multiple nutritional deficiencies.

Shock was a prominent clinical feature in a number of the cases reviewed in this report but it is impossible to estimate what part, if any, this factor played in the development or aggravation of liver injury. It is well known that liver function may be profoundly altered by shock, presumably because of hypoxia with reduction in hepatic blood flow.[24] Such a condition might well produce further injury when antecedent liver damage exists.

Anatomic Changes in the Liver.—

Livers damaged by hepatic necrosis exhibit a wide variety of pathologic changes which may or may not indicate the nature of the noxious agent.[4, 25] The finding of histologic alterations which are not typical of either viral or toxic necrosis may make the establishment of an etiological diagnosis difficult if not impossible. In patients who die of eclampsia the characteristic pathologic changes in the liver may be absent entirely.[26] Although the majority of our cases in which autopsy data were available presented hepatic changes consistent with eclampsia, the clinical and pathologic findings in 3 cases were more typical of fulminating viral hepatitis with hepatic necrosis. We detected no case comparable to Sheehan's "obstetric acute yellow atrophy,"[27] where necrobiotic change was absent.

Summary and Conclusions

In 21 of 1,200 obstetric deaths reviewed by the North Carolina Committee on Maternal Welfare, hepatic failure was apparently a primary or contributory factor in the cause of death. These figures indicate that liver injury is a definite hazard in pregnancy.

The pregnant woman is subject to various factors known to precipitate hepatic damage—acute toxemia, anesthetic agents, infection, nutritional insufficiency, hemorrhage, and shock. In several of the 23 cases presented, more than one factor was involved. In Case 23, for example, liver injury was preceded by toxemia and chloroform anesthesia. The obstetrician must be cognizant of these various etiological factors and must anticipate their possible cumulative action.

Once extensive liver injury has occurred, the results of treatment are doubtful. Accordingly, every effort must be directed toward preventing possible damage to the liver by the maintenance of adequate nutrition, early and vigorous treatment of toxemia, and scrupulous avoidance of hepatotoxic agents during pregnancy.

The appearance of jaundice during pregnancy is to be regarded as an extremely dangerous sign.

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Discussion

DR. H. CLOSE HESSELTINE, Chicago, Ill.—The fact that hepatic failure was diagnosed 21 times in 1,200 deaths (a rate of 1.7 per cent) indicates its rarity. It is a tremendous task to catalogue correctly the primary causes of deaths of such number. As you realize, the presence of multiple factors among cause of death requires careful study for fair judgment.

Dr. Lock did not indicate how many years were involved to produce this total number of deaths, nor did he state the ratio of deaths to deliveries. This oversight is understandable because there were more points than could be discussed properly in the allotted time.

We are all aware of the tremendous improvements that have occurred in maternal mortality in the United States in the last 15 to 17 years. Our efforts have begun to bear fruit. Indeed, it is very easy to talk about good results and these are positive points. It is, however, also a positive approach when we take up failures in a constructive way. Improvement occurs in one of several ways, as by accident, trial and error, intention, persistence, and so on. With the record of our past experiences and knowledge of our present day, one has some license to prognosticate the future.

Fatalities are cold, clear-cut facts. The causes of death, however, are not always so exact. Perhaps some of the cases may have had liver damage as a primary factor, while in others, presumably, it could have been secondary. If a hepatic lesion is the primary factor, then it is significant. If it is a resultant factor, then we must be able to interpret it and approach it appropriately.

There are a number of corollaries in medicine which produce secondary factors. An illustration may be that of shock and hemorrhage. The shock may be totally or partially corrected, but the shock may have been so profound and so damaging that the patient may die a day or so later because of irreversible changes. Dietary factors and improper care of a critically ill patient sometimes provide the strain that is unbearable rather than the primary disease.

Because of the rapid reduction in maternal deaths there will be fewer fatalities to study in the future. To be philosophical about this problem, any deaths are too many. For that reason, any death is a failure, a failure because we have not yet advanced scientifically to the point of being perfect. We probably never shall be perfect, but perfection should be our goal.

At the Chicago Lying-in Hospital we have not had a sepsis death since 1940 although we have escaped narrowly in several instances. Deaths from hemorrhages have been eliminated of late. There have been a few deaths from nephritis, heart disease, embolism, and other conditions.

Perhaps the future will witness better diagnostic means for evaluation of hepatic function which will indicate minor degrees of injury. The histological changes are not available routinely except post mortem. Those biopsies taken in life are limited because our access to the liver even by peritoneoscopy is limited.

I wish to ask Dr. Lock and his colleagues what therapy is recommended either prophylactically or therapeutically in patients with liver injury.

DR. D. M. LOW, Toronto, Ont.—Like many others in our specialty I have not been impressed by the occurrence of serious hepatic dysfunction in pregnancy. Possibly we have not observed our patients closely enough for this evidence, but in thirty years of practice I cannot recall a private patient with either a normal or toxic pregnancy showing evidence of hepatic failure sufficient to be alarming or cause mortality. It is, therefore, somewhat surprising to read of an incidence of 21 cases (1.7 per cent of 1,200 maternal deaths) as found in the records of the North Carolina Committee on Maternal Welfare. It is just another instance of the value of such committees which we in Canada have been backward in establishing. It would be interesting to know over what period of time the 1,200 maternal deaths took place. Even placing the maternal mortality as low as 2 per 1,000 births the 1,200 deaths would mean that there had been 60,000 births among which there were 21 maternal deaths where hepatic failure was the main cause of mortality. It is obvious that with only 1 death from this cause in every 30,000 pregnancies it would be very difficult for any one group or area to have enough clinical material to carry out any very intensive study or research.

However, Dr. Lock and his associates have produced a very worth-while survey of these 21 cases, labeling 9 in Group A as primary hepatic disease and 12 in Group B as showing evidence of extensive hepatic injury associated with severe toxemia of pregnancy.

According to the data supplied regarding Group A, it would appear that the first 5 cases listed in this group showed evidence of toxemia, and that only 4 might be considered as cases of primary hepatic disease. Further elucidation on this point would be appreciated.

Dr. Lock has made an extensive review of the literature and has noted particularly the association of hepatic necrosis and pregnancy and underlines the importance of the so-called trophopathic factor, as expounded by Himsworth and others. This concept of a suboptimum standard of nutrition over a long period of time prior to and during a pregnancy giving rise to a "conditioning" or weakening of the liver function should reveal at autopsy a large fatty liver showing evidence of increased fibrosis as well as necrosis. The work of Chester Jones on the effect of diet in the regeneration of the fatty liver of alcoholics, deprived of alcohol, is very convincing. In occupied France during the last war with the deprivation of alcohol the diseases and neuritis due primarily to alcohol decreased, but since the standard of nutrition also suffered it was found that cases of cirrhosis of the liver increased. This again emphasizes the importance of proper nutrition.

The detail of autopsy and laboratory examination in the 4 cases outlined is excellent and should stimulate similar study in such cases. In Case 1 the finding of a small liver and massive necrosis without increase in fibrosis indicates an acute castastrophe of unknown origin not due to any deficient standard of diet.

As regards treatment, no suggestion is made of any specific therapy being available. Indeed, the almost certain mortality in these acute cases only advertises the universal ignorance of the profession as a whole as regards etiology of hepatic necrosis.

This paper of Dr. Lock and his associates serves to bring to our attention a very rare but serious situation arising in pregnancy. It should mean that we must regard jaundice from any cause arising in pregnancy as a very dangerous sign.

DR. JAMES QUIGLEY, Rochester, N. Y.—Dr. Lock's paper has brought to our attention an unusually large number of pure cases of hepatic failure. Fourteen of the cases

could be included as eclampsia or rather as ordinary toxemia in which the liver damage is not unusual, but nine of these cases are pure cases of hepatic toxemia. I should like to ask Dr. Lock as to the correlation of prenatal care in these cases. I think with our marked drop in maternal mortality, we have become a bit complacent about lay education and I know in my community we have had a return to a few deaths from toxemia which should not have occurred. Perhaps we shall have to return to lay education in order to get the patients to the physician or to the clinic early in pregnancy.

DR. HAROLD MACK, Detroit, Mich.—Dr. Lock's report on hepatic failure in pregnancy has been of special interest to me since during the course of our study of plasma protein in normal and complicated pregnancy we have had the opportunity to observe three patients with liver damage, two with severe cirrhosis, and one with hepatitis originating in the pregnancy. None of these cases was fatal.

The plasma proteins were analyzed by the electrophoretic technique, a new and highly accurate method which permits a more detailed study of various protein fractions than is possible by the ordinary laboratory methods. I would like to show the characteristics of the electrophoretic patterns of one of our cases of severe hepatic damage because it demonstrates the effects of liver injury upon the composition of the blood proteins in pregnancy.

In cirrhosis we find that the albumin is lower than in the normal pregnancies and that the total globulin area is greater. In other words, reversal of the AG ratio has taken place. The most striking feature of the plasma protein pattern in cirrhosis, however, is the marked elevation of the gamma globulin peak. In cirrhosis the elevation is pathognomonic of liver damage. In this case the gamma globulin fraction comprised one-third of the total plasma protein. In more severe hepatic injury, as reported by others, it may constitute even a greater proportion of total blood protein. It is important to remember that the gamma globulin fraction contains most of the antibodies liberated from the reticuloendothelial system by adrenal cortical stimulation.

In the patterns of these patients post partum we see that although there has been some improvement in the albumin, the gamma globulin peak still continues high; that is considered a sign of poor prognosis. It is interesting to compare this pattern of liver damage with the blood patterns observed in pre-eclampsia and eclampsia. Severe toxemia also produces albumin deficiency in the blood and an increase in the total globulin. In toxemia, however, we found that the globulin increase is due largely to an increase in fibrinogen which is formed by the liver whereas the antibody-containing gamma globulins in toxemia of pregnancy are actually depressed. This may explain why the toxemic patient seems to be more subject to infection than others. It would appear that if toxemia is related in any way to liver dysfunction it does not manifest itself in the blood in the same way as does liver necrosis, and that if hepatic necrosis is a feature of nonfatal eclampsia it does not provoke the same response in the blood protein picture as do other forms of liver damage, such as cirrhosis and hepatitis. I think the work of Dr. Lock and his associates is most important and I am sure that a great many subclinical and nonlethal grades of liver damage exist which should be studied more intensively.

DR. LOCK (Closing).—Dr. Low has noted that hypertension and albuminuria were present in some of the patients who were classified as having primary hepatic failure. In each instance the prenatal record showed that these findings were absent prior to the onset of the hepatic disease. Hypertension and albuminuria are known to be associated with primary hepatic disease.

Since all maternal deaths in North Carolina are reviewed by our Committee, the mortality from primary liver disease during pregnancy can be roughly estimated for our geographic area from this study. The 21 cases reviewed in this study were reported during a period in which we analyzed 1,200 deaths from all causes occurring in women who were pregnant or had been delivered within six months prior to death. During this six-year period approximately 650,000 births were recorded in North Carolina.

We were impressed by the fact that marked liver injury was found at autopsy in patients who died of toxemia of pregnancy and apparently had had no clinical evidence of liver injury. In these cases the toxemia was rapidly progressive and resistant to ordinary forms of treatment. Liver damage must be suspected in cases of severe progressive toxemia, whether or not clinical evidence of hepatic impairment is present. If careful autopsy studies could be performed in a higher percentage of patients who die of toxemia, the incidence of liver failure could be better evaluated and the general nature of the problem would be more clearly understood.

Dr. Quigley has asked about the prenatal care these patients received, and whether any preventive measures are effective. Their prenatal care was not ideal; several of the patients with toxemia of pregnancy and all of those who had hypertensive cardiovascular disease with superimposed toxemia had refused advice to enter a hospital at some time prior to their final admission in the acute phase of the illness.

The importance of adequate nutrition in pregnancy has not been emphasized sufficiently in relation to this problem. The experimental evidence of Himsworth and others is convincing.

We do deal in North Carolina with a group of people who are inclined to have very poor nutritional and dietary habits. Some patients in our wards give a history of having existed on white gravy, cornbread, and beans and refuse an attractive tray containing fresh fruit, vegetables, and milk saying, "We don't eat that stuff." They are not a particularly underprivileged group, but they have dietary traditions. In our own clinic we have gone to great lengths to have classes in diet, and to teach our service patients that they must drink some of the milk and eat some of the fresh vegetables and meat instead of selling them all.

We are intensely interested in our local nutritional problems and are beginning an investigation of their relation to pregnancy, and to hepatic failure in particular.

THE BULBAR CONJUNCTIVAL VASCULAR BED IN NORMAL PREGNANCY*†

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(From the Departments of Obstetrics and Gynecology and Medicine, New York Hospital, and Cornell University Medical College)

WITHIN recent years further evidence has accumulated to indicate that there are widespread vascular changes associated with the toxemias of pregnancy. Hertig,[1] Sheehan,[2] and Falkiner[3] have carefully examined various organs in eclampsia obtained at autopsy. Fundamental vascular disturbances which apparently underlie the observed changes in toxemia have been noted in many organs, particularly in the kidney, liver, and brain. Hertig[1] states that in all lesions there is a change in the wall of the terminal arteriole from which the capillaries arise. This degenerative process leads to obstruction of the vessel and ischemic necrosis of the surrounding tissues. Sheehan[2] has recently described in detail the extensive spasm in the afferent arterioles which presumably produces the renal changes found in toxemia complicated with bilateral renal cortical necrosis.

Recent published studies from our department[4] have indicated that there are observable retinal arteriolar changes in more than half of the patients with the more advanced forms of toxemia. A frequent important retinal observation in the severe toxemia was generalized arteriolar spasm. The ophthalmoscope with a magnification of 16× permitted observations of only the large arteriolar branches of the ophthalmic artery. In a large series of normal pregnancies in the New York Lying-In Hospital, Snyder[5] found little or no change in the arterioles and venules observed in the retina. Because of the limitations of magnification and light no information concerning the smallest vessels was obtained.

Observations of small vessels in toxemia have been carried out by several investigators on the nail bed, using direct biomicroscopy.[6-10] The interpretation of these changes is difficult because the anatomic nature of the nailfold vessels and their relationship with the remainder of the vascular bed are obscure. They are capable of contraction and hence are perhaps more comparable to arterioles rather than to true capillaries. However, rather than giving origin to true capillary vessels, as do the terminal arterioles, the nailfold vessels seem to function more in the manner of contractile direct channels, connecting the arteriolar

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and venular tree of the subcapillary plexus.[11] Because of the unusual nature of the nailfold vessels, and difficulties in directly visualizing more than short vessel segments, we searched for techniques which would permit biomicroscopic studies of more complete peripheral vascular systems.

We found that recently Lee and Holze[12] had devised methods for studying the physiology of the human capillary bed by using the peripheral vascular system in the bulbar conjunctiva. In this tissue a complete peripheral vascular network, including arterioles, true capillaries, and collecting venules, can be readily observed at relatively high power in the unanesthetized subject. With routine biomicroscopic equipment and the use of certain objective criteria for measuring reactive and dynamic changes in the peripheral vessels, it has proved possible to establish several functional changes as well as morphologic abnormalities in the conjunctival capillary bed in hypertensive disease. The techniques have been adapted to the evaluation of changes in these vessels during pregnancy. Previous studies on blood flow in the conjunctival vessels in pregnancy have been carried out by Odell[13] and Zilliacus.[14] These workers, however, devoted their attention to the character of red cell flow, which they describe as blood sludge, and they have not reported any physiological evaluation of the peripheral vessels, per se. The formation of sludge has been attributed by these authors to changes in the intravascular contents without reference to possible important physiological alteration in the vessels themselves. It is the purpose of this report to describe some striking variations that occur in the reactivity and in the inherent hemodynamic state of the peripheral vessels in normal pregnancy.

Method of Study

The vascular bed of the lateral bulbar conjunctivae is observed with the slit lamp and a binocular microscope. A magnification of 50× is found most satisfactory for routine repeated observations. For limited detailed inspection a magnification as great as 144× may be used. However, at such high magnifications the greatly reduced field of vision, the limited light, and the movements of the eye seriously handicap the observer. All pictures are made with a 35 mm. reflex camera using an F2.0 lens. The photographs are taken directly through the barrel of the microscope leaving the ocular in place. The camera is supported on a metal platform which allows it to slide backward and forward as the microscope is focused on the eye vessels. The light source used for focusing is that of the slit lamp itself. When the desired area and vessels are in focus the shutter speed is 1/50 of a second; this is synchronized with a 180 watt-second strobe light unit, at a distance of 12 to 18 inches from the eye.

The rate of blood flow in representative arterioles, venules, and capillaries is determined with an ocular micrometer and a fast stop watch. At a magnification of 50× the blood flow is over 50 spaces (0.10 mm.) of an ocular micrometer. The data are then recalibrated in millimeters per second. Various dilutions of epinephrine are instilled into the conjunctival sac to determine the minimal concentration which produces threshold vasoconstriction of arterioles and precapillaries, and slowing of the venular flow at various stages of pregnancy.

Fig. 1 indicates diagrammatically some of the more important conjunctival vascular findings observed during pregnancy, labor, and the puerperium. Arteriolar spasm, capillary tortuosity, granularity of flow, and capillary ischemia are divided arbitrarily into three grades. Grade III, arteriolar spasm, is not

seen in the normal pregnancy and appears only rarely in advanced toxemia. Grade II spasm represents true bowel formation in the arteriolar wall. Grade I, as indicated in Fig. 1, is a milder variety of spasm. The normal vessels show an undulating activity which is described as vasomotion. This represents the spontaneous variation in caliber of these vessels resulting from contraction and relaxation of the smooth muscle. It is usually irregular in rate and degree and in the duration of the dilated and constricted phases. Capillary tortuosity (Grades 0 and I) does not change during the course of normal pregnancy; Grades II and III are found primarily in prolonged marked essential hypertension. Grade III granularity and capillary ischemia are evident in normal pregnancy in the third trimester, during labor, and the first week post partum.

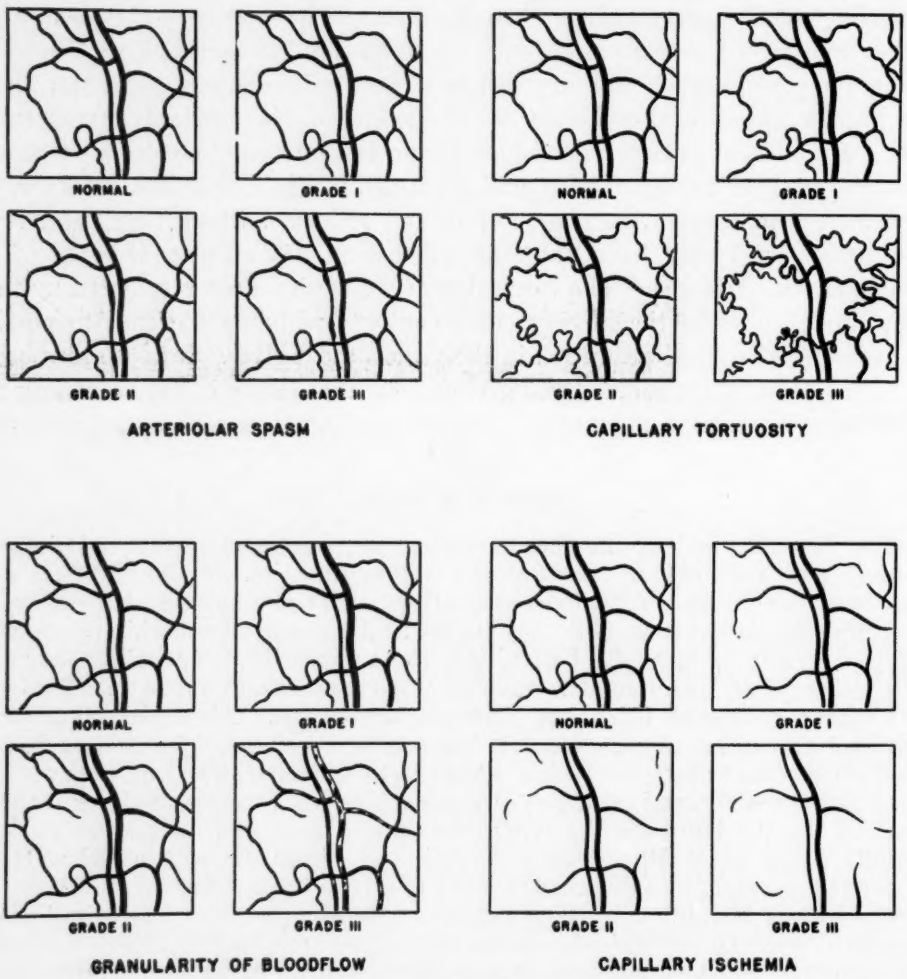

Fig. 1.—Vascular changes in bulbar conjunctiva.

Eighty-five normal pregnant women, 46 primiparas and 39 multiparas, at the New York Lying-In Hospital, were studied by these methods at bimonthly intervals on the average, during their entire gravidity. The data collected included numerous repeated observations in the three trimesters of pregnancy. These observations became even more frequent during the last eight weeks of pregnancy at which time the conjunctival vessels appeared to change most

rapidly. Because of the importance of the findings during labor, observations were similarly made on the delivery floor at varying intervals during the course of labor. The biomicroscopic studies were carried out by all of the authors, whose independent notations on the same patients proved to be in close agreement.

Results

During the course of normal pregnancy progressive changes are noted in the conjunctival vessels. The caliber of the arterioles, the speed of flow, the number of capillaries, the presence of capillary tortuosity, and the average epinephrine sensitivity are indicated in Tables I and II. The multiparas and primiparas were studied separately to determine whether there is any real difference in the vascular bed. This study was extended to several grand multiparas. Multiparity does not influence the extent of vascular change provided that all previous pregnancies were classified as normal.

TABLE I. CONJUNCTIVAL VASCULAR CHANGES IN NORMAL PREGNANCY

GRADE	ARTERIOLAR SPASM	GRANULARITY OF FLOW	CAPILLARY ISCHEMIA	CAPILLARY TORTUOSITY	EPINEPHRINE REACTIVITY
First trimester	0	0	0	0-1	1/50,000
Second trimester	0	0-1	0-1	0-1	1/100,000
Third trimester	0-1	1-2	1-2	0-1	1/200,000
Labor	0-1+	2-3	2-3	0-1	1/400,000
First week post partum	0-1	1-2	1-3	0-1	1/100,000
Six weeks post partum	0	0	0	0-1	1/50,000

TABLE II. RATES OF BLOOD FLOW IN NORMAL PREGNANCY

MILLIMETERS PER SECOND	ARTERIAL	VENULE	CAPILLARY
First trimester	.0917	.0598	.0559
Second trimester	.0830	.0458	.0395
Third trimester	.0535	.0429	.0350
Labor	.0523	.0313	.0252
Post partum 1 week	.0529	.0436	.0379
Post partum 6 weeks	.0952	.0606	.0575

During the first trimester of normal pregnancy the conjunctival circulation exhibits no significant differences from that of the normotensive nonpregnant adult. Fig. 2 illustrates a representative vascular pattern. The main arteriole and venule are well filled. There is no arteriolar spasm and no capillary tortuosity. The capillaries are numerous and although an occasional vessel may be partially filled and granular, the vast majority are well filled and the blood flow is rapid. The blood flow in the larger arterioles is so rapid that it may be difficult to follow.

From the fourth through the sixth month of pregnancy gradual peripheral vascular changes make their appearance. The first striking difference is the slowing of the blood in the capillaries and finer venules. This reduced speed of flow is characterized by a granular appearance (Grade I) which involves particularly the blood column in the finer venules. Occasional capillaries disappear completely from view because of the absence of blood in the lumina. Other capillaries exhibit irregular filling with stagnant red blood cells. The large veins and the entire arterial system, arterioles, and precapillary arterioles, continue unchanged. The arterioles demonstrate the usual variety of vasomotion without any real spasm.

These changes in the bulbar conjunctival circulation seen in the second trimester increase progressively in the last months of pregnancy and become maximal in the final weeks prior to term. The capillary blood flow is further

reduced. The ischemia (Grades I and II) spreads to involve large areas of the microscopic field in which no vessels are visible. This may be so striking in some patients that it may even be seen grossly without the microscope. The remaining capillaries show slowed or stagnant red blood cells. Several capillaries may exhibit average filling and speed of flow but these active vessels are usually

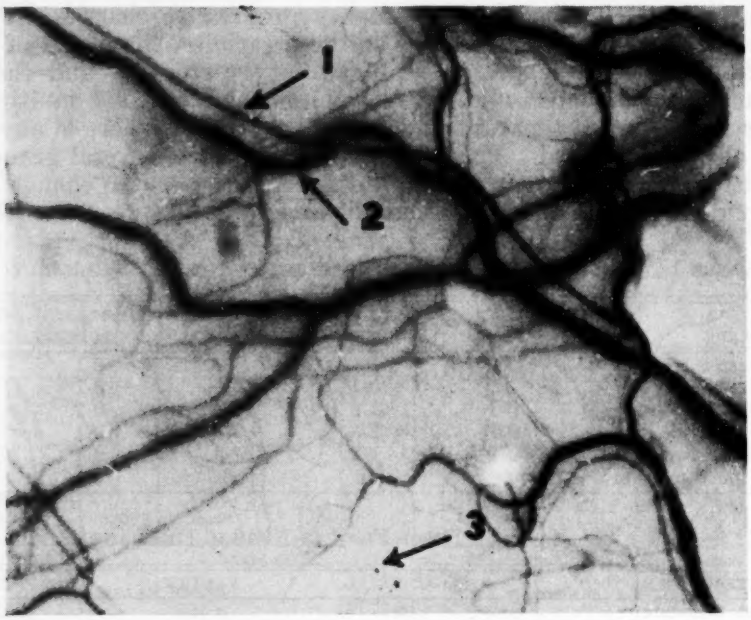

Fig. 2.—Normal nonpregnant or first trimester (*1*) arteriole, (*2*) venule, (*3*) capillary. (Magnification ×150.) (Reduced one-third.)

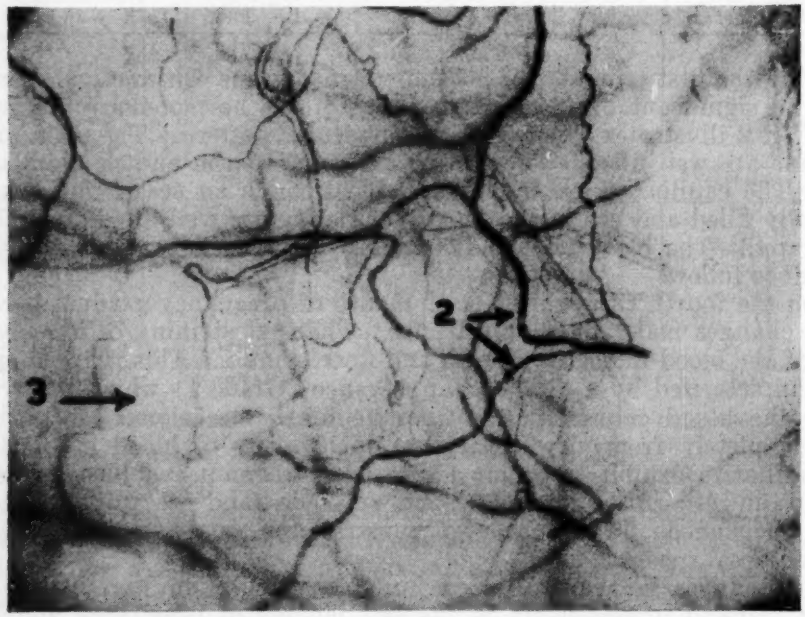

Fig. 3.—Normal third trimester (*2*) venule, (*3*) capillary ischemia. (Magnification ×150.) (Reduced one-third.)

preferential channels passing the blood directly from a fine metarteriole into the collecting venule. This slowing of flow which is so easily seen in the capillaries and veins is likewise apparent in the arteriolar system. In the metarterioles the slow flow is easily observed and segmentation of the red cells may be visualized. This phenomenon gradually spreads as the pregnancy pro-

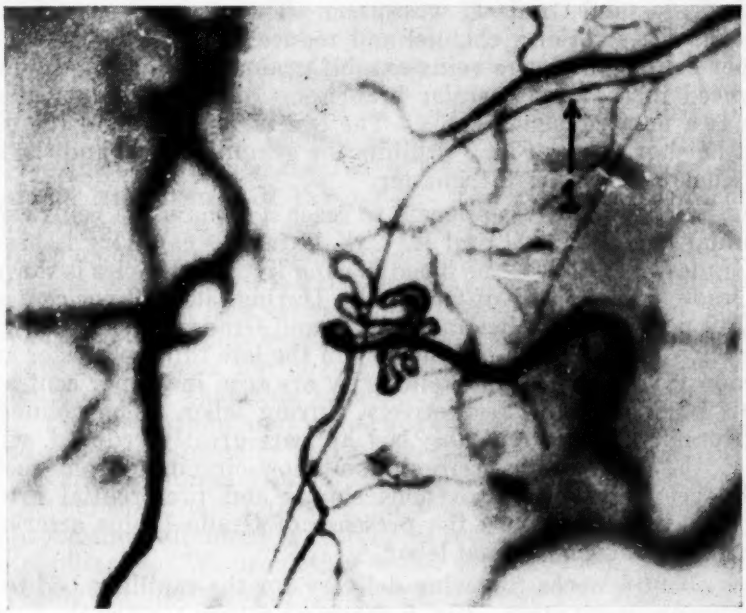

Fig. 4.—(*1*) The maximum arteriolar spasm seen in the late third trimester and labor. (Magnification ×150.) (Reduced one-third.)

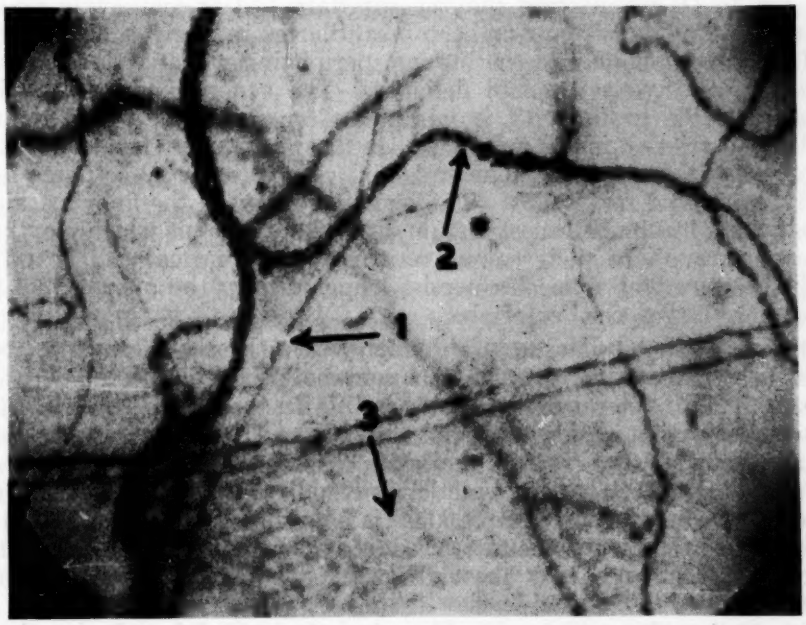

Fig. 5.—First week post partum (*1*) arteriolar segmentation, (*2*) venule granularity, (*3*) capillary ischemia. (Magnification ×150.) (Reduced one-third.)

gresses in retrograde fashion to involve somewhat larger arterioles. In normal pregnancy, however, this process generally does not extend to the arterioles of the conjunctiva with a diameter greater than 30 to 40 μ. Vasomotion also begins to increase rapidly close to term. These rhythmical fine waves of constriction and relaxation are more prominent in the finer arterioles. In the last month of pregnancy 58 per cent of normal cases exhibit a Grade I and 26 per cent show Grade I plus and Grade II vasospasm. The waves of constriction appear to compromise the arteriolar channel and reduce the diameter of the lumen by about 25 per cent. The large veins exhibit granularity of blood flow which is more advanced in the finer venular branches. In most patients at about this time there is a marked photophobia. The eye tears easily and the observation times must be shortened. Fig. 3 exhibits the granular veins and the increasing capillary ischemia of the third trimester.

During labor this process appears to reach a climax; the veins exhibit maximum granularity (Grades II and III), the extensive capillary ischemia is generalized (Grades II and III), the blood flowing in the arterioles is slowed by true spasm of Grade I, and rarely of Grade II. During labor 73 per cent show some spasm and 40 per cent exhibit Grade I plus and Grade II arteriolar spasm. All patients develop ischemia and granularity in the late third trimester and during labor. Grade III ischemia and granularity are seen in 53 per cent and 40 per cent of this normal group, respectively, during labor. The volume of blood filtering through the true capillary bed appears greatly reduced, with the remainder of the conjunctival circulation short-circuited from metarterioles through the venules via arteriovenous shunts and preferential arteriovenous channels. Fig. 4 demonstrates the presence of Grade I plus arteriolar spasm a day prior to the onset of normal labor.

It takes about 6 weeks following delivery for the capillary bed to return to the normal prepregnant state. Fig. 5 shows no return toward the nonpregnant vascular picture on the third day post partum. The arteriole is attenuated and shows segmented flow related to the marked slowing. The large venules exhibit Grade II granularity and the capillary bed is completely blanched in some areas. Gradually the number of capillaries in a given area increases as the red blood cells pour into the lumina, permitting visualization of empty vessels which are present prior to delivery. The venous flow rapidly increases its speed and the granularity is minimal after one week post partum. The arteriolar constriction is the first factor to disappear after labor. By the third day any spasm is completely gone and mild vasomotion may be noted as during the early months of pregnancy. The segmented flow in the finer arterioles usually disappears by the fifth postpartum day. These vessels which may have been constricted throughout their course return to their normal caliber. The variations in the terminal arterioles persist longer during the puerperium than the changes in the larger-sized arterioles.

During the first trimester of pregnancy the threshold response to diluted epinephrine occurs on the average at a concentration of 1/50,000 which is comparable to that for the nonpregnant normal.[12] In the second three months there is a gradual elevation in this threshold response to 1/100,000 epinephrine, and in the third trimester the vessels similarly constrict at 1/200,000 to 1/400,000 epinephrine. During labor the reaction is usually above 1/400,000 and in many instances a strong reaction at 1/500,000 is obtainable. By the sixth to seventh postpartum day the responsiveness is reduced, depending on the individual sensitivity prior to delivery. By the sixth week post partum the epinephrine reactivity returns to the normal level.

Table II lists the average rate of conjunctival blood flow during the various indicated periods for ten normal pregnant patients. The speeds found during

the first trimester and six weeks post partum approximate the levels obtainable in the nonpregnant normotensive woman. As pregnancy progresses through the second and third trimesters there is gradual reduction in the rate of blood flow. During labor blood velocity is about one-half that of the normal nonpregnant state. In some cases a return toward normal flow speeds occurs during the first week post partum. There is some tendency for the speed of flow to be slightly faster at 6 weeks following delivery than during the first trimester.

Comment

The conjunctival vascular bed is undergoing continued progressive changes during the course of normal pregnancy. The slowing of the blood, which can be quantitatively measured in various-sized vessels, is associated with a granular appearance of the moving blood. Knisely and his group[15] describe the granular flow as "sludge"; and Odell, Aragon, and Pottinger,[13] studying this phenomenon in pregnancy, refer to this same process. Knisely[15] believes that the blood cells are fixed together in masses by increased stickiness and cohesiveness of the cell surface. These authors also suggest that there is a causal relationship between this sludging and the increase in sedimentation rate and plasma fibrinogen. There is considerable evidence to refute the point of view that this so-called sludge is adherent masses of red blood cells. Fowler[16] stimulated cervical sympathetic ganglion of the cat on one side and produced granular blood flow in one eye only which returned to normal in several minutes. Lutz, Fulton, and Akers[17] produced apparent sludge in the hamster; when these groups of erythrocytes were compressed by a microprobe the individual erythrocytes separated completely and passsed singly into capillaries. When another vessel was cut by a microknife, packed erythrocytes moved individually and escaped into the tissues without evidence of increased intravascular adhesiveness. Although Odell, Aragon, and Pottinger[13] found elevated sedimentation rates when granularity was most marked, in two cases of eclampsia the excessive "sludging" was associated with normal sedimentation rates. Zilliacus,[14] and Hirschboeck and Woo[18] also noted that in 10 to 20 per cent of cases the degree of clumping did not correspond to the sedimentation rate. We were able to produce marked granularity in pregnant and nonpregnant patients by dropping 1/10,000 epinephrine into the conjunctival sac. After several minutes this is completely reversible; marked slowing of all blood flow is associated with the granularity. It is also true that granularity occurs in normal nonpregnant patients[19] in small limited areas of the conjunctival vascular bed during localized "constrictor" phases of spontaneous vasomotor activity. It is therefore our impression that "granular" blood flow which appears as "sludge" in the conjunctiva of normal pregnancy is primarily related to a slowing of the blood flow. This latter is principally brought about by an increase in vasomotion and minimal spasm of the finer end arterioles and metarterioles, rather than adhesiveness of the red cells. Changes in blood constituents such as the proteins may, of course, in certain disease entities, be a possible factor in inducing red cell aggregations.

During normal pregnancy, Coryell and associates[20] have studied the changing distribution of the blood plasma proteins. The albumin and gamma globulin progressively fall to the time of delivery and the alpha, alpha 2, beta globulin and fibrinogen rise at the same time. After delivery these protein fractions return toward the prepregnant level. As a result of the above the albumin-globulin ratio progressively falls until delivery and returns toward the normal 6 weeks post partum. The conjunctival vascular changes, slowing of blood flow, ischemia of the capillary bed, granularity of blood flow, and spasm of arterioles, are maximum at the time of delivery, similar to the blood protein

changes. There is no positive evidence, however, of a direct causal relationship. In cirrhosis of the liver, for instance, there is a reversal of the albumin-globulin ratio and an elevated globulin; slowing and granularity of flow are visualized in the bulbar conjunctiva. The capillary ischemia and arteriolar spasm seen in normal pregnancy, however, do not occur and instead there is arteriolar dilatation.[21]

The reduced effective perfusion of the capillary bed is another major progressive change in the conjunctiva of pregnancy. Particularly during the last trimester the number of capillaries containing moving blood is reduced, and a few may show stagnant red blood cells only. Immediately before and during labor this profound ischemia reaches its height, to recede gradually during the first month post partum. The diminished circulation is produced by a reduction of the arteriolar lumina which supply the capillary bed and a slowed velocity of arteriolar (and capillary) flow. The ischemia is so outstanding that these factors alone seem inadequate to explain it completely. In addition, it is therefore possible that a good portion of the circulating blood may be bypassing the peripheral vascular bed, shunted through arteriovenous channels which lie more proximal than the vessels apparent in the conjunctiva. Is this ischemia related to a generalized peripheral reduction in blood flow with the shunting of large quantities of blood to the uterus? This may be determined in the future by similar vascular-bed studies of other organs during pregnancy.

The granularity of the veins and the ischemia of the capillary bed which are gradually increased in the later weeks of pregnancy appear to be directly dependent on the arteriolar changes which occur concomitantly. The reduced caliber of the arterioles, the increase in vasomotion, the early spasm during labor, and the segmented arteriolar blood flow are clearly visualized in the conjunctival vessels repeatedly and consistently by different observers. This change in the arterioles appears responsible, in large part at least, for the more obvious alterations in flow through the capillary bed and venous channels. Whether said changes are limited to the conjunctiva and skin, or whether they involve the internal viscera, will be decided by future investigations. Bartholomew[22] has indicated that frequently edema, elevation of blood pressure, and albuminuria occur during labor preceded by a normal pregnancy. This is suggestive evidence that widespread vascular changes are taking place in other parts of the body during normal pregnancy.

Recent studies of blood flow in the liver[23] and brain[24] show normal values in uncomplicated pregnancies. These determinations are made possible by the application of the Fick principle. This postulates that the quantity of any substance taken up by an organ from the blood which perfuses it is equal to the total amount of the substance carried to the organ by the arterial inflow less the amount removed by the venous drainage during the same period of time. Although these determinations may give an accurate picture of the blood flow, the exact distribution of this flow is not obtained. The activity of the capillary bed, the rate of flow in the capillaries, and the proportion of blood coursing through the arteriovenous channels are completely unknown after such blood flow determinations. The various changes in the vessels of the conjunctival vascular bed with the marked slowing of the arteriole circulation, the capillary ischemia, and the venous granularity all indicate a gradual reduction in blood flow in this portion of the peripheral vascular bed. Although the blood-flow changes in liver and brain do not suggest any reduction of blood supply in these organs, vascular redistribution may occur in these organs as is observed in the conjunctiva in normal pregnancy by the interruption and short-circuiting of blood via arteriovenous channels.

Lee and Holze[12] find the epinephrine threshold in normotensive individuals to be in the range of 1/20,000 to 1/50,000. In essential hypertension the aver-

age response is 1/400,000. In normal pregnancy the conjunctival vessels become increasingly sensitive to epinephrine as the gravidity progresses. The reactivity is highest during the ninth month at the period when the incidence of toxemia is maximal and likewise when the blood pressure rises even during the normal antepartum course. It may well be that comparable biological vasotrophic factors are present in both these conditions to produce concomitant blood pressure elevation.

Assali and his co-authors[25] have recently investigated the effect of one of the autonomic blockading drugs, tetraethylammonium chloride, on the blood pressure in normal and toxemic pregnancies. In pre-eclampsia at about the twentieth week of pregnancy there is a substantial reduction of the effect from TEAC, and the blood pressure does not fall to the same extent as in normal pregnancy. This difference in response suggests that there is a shift from neurogenic vascular tone to a greater hormonal control of peripheral blood vessels in the middle of the second trimester. It is of interest that in the bulbar conjunctiva in normal pregnancy there is, at about this time, the first important change in the vascular bed. A noticeable reduction in rate of blood flow, visible generalized granularity of flow, particularly in the smaller venules, and increasing ischemia of the capillary bed are easily detected. At about the twentieth week there is an increased sensitivity to topically applied diluted epinephrine. Our findings in the conjunctival vascular bed and Assali's observations following automatic blockade add further evidence indicating that striking variations in the vascular bed in the second trimester may possibly be mediated at least partly by hormonal changes.

Conclusions

1. With the slit lamp and a binocular microscope repeated observations may be made of the conjunctival vascular bed during pregnancy by a simplified technique and without discomfort to the patient.

2. Throughout pregnancy there is a progressive reduction in the rate of blood flow in the veins, arterioles, and capillaries. This is most easily observed in the venules and is characterized by granularity. In the finer arterioles the slowing produces a characteristic segmentation of flow.

3. The active capillary bed of the conjunctiva shows a progressive reduction during pregnancy. Late in the third trimester and during labor this is characterized by an advanced tissue ischemia.

4. A diminution in capillary blood flow and a reduction in the number of visible capillaries is partly related to the slower rate of flow in the larger vessels and in part to the channeling of blood via the arteriovenous connections.

5. As pregnancy progresses there is an increase in the vasomotor activity of the finer arterioles.

6. Late in the third trimester, and particularly frequently in labor, a true spasm (Grades 0 to II) may be observed in the conjunctival arterioles. This spasm may be present for as long as forty-eight hours post partum.

7. A progressive increase in the sensitivity of conjunctival vessels to epinephrine occurs during the course of pregnancy, is maximum at the time of labor, and diminishes during the first week post partum.

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Discussion

DR. E. D. COLVIN, Atlanta, Ga.—More than fifteen years ago, under the instruction of Dr. A. V. Hallum, as an Ophthalmological Consultant, we familiarized ourselves with the interpretation of retinal findings in pregnancy. This knowledge has been invaluable in the diagnosis and management of hypertensive vascular disease and true toxemia complicating pregnancy.

In this discussion, I wish to call attention to the striking parallelism of the bulbar conjunctival findings as described in the authors' paper and certain of the retinal findings which we have noted during the course of normal pregnancy; also to the relation which these ocular findings may bear to the high frequency of proteinuria which we have found to develop during labor.

The ophthalmoscopic retinal findings are not strictly comparable with those of the bulbar conjunctivae, due to the fact that the ophthalmoscope affords much less magnification than the device used by the authors and the range of visibility covers only the larger vessels and does not extend to the very fine peripheral branches. Notwithstanding this difference, the vascular behavior, as viewed in the two ocular areas, appears to be due to a common factor which is able to affect the finer vessels of the bulbar conjunctiva in more ways and to a greater degree than the larger vessels in the region of the optic disc.

The ophthalmoscope cannot disclose "vasomotion and granularity" which, we are told, are best seen in the very small terminal arterioles for the reason above mentioned, but does demonstrate the fact that a very mild disturbance of the arteriovenous ratio and degree of increased light reflex early in pregnancy becomes more distinct and pronounced in the ninth month of pregnancy along with a rise in blood pressure and possibly a trace of proteinuria. On routine retinal examinations during pregnancy we have occasionally noted that the retinal findings may change during the course of pregnancy, a normal arteriovenous ratio becoming definitely disturbed and a light reflex developing or becoming definitely increased. This is analogous to the development of spasms, "vasomotion," and "granulation" in the minute arterioles, as described by the authors. In each case there must be an underlying spasmogenic factor which is increasingly activated in the ninth month and particularly in labor.

We have found that a high frequency and significant degree of proteinuria develop during labor and since the degree of proteinuria can be correlated with development of acute placental infarction and progressive breakdown in the chorionic epithelium we are justified in postulating that the same spasmogenic factor (oxytocin ?) may not only initiate labor by acting on the smooth muscle of the uterus but also initiate toxemia during labor by acting on the smooth muscle of the sphincters of the placental veins and set in motion a sequence of fetal and intervillous vascular effects eventuating in localized placental necrosis (Bartholomew, R. A., et al.: AM. J. OBST. & GYNEC. 62: 246, 1951). Therefore, in this respect there is a suggestive analogy, namely, that these vascular phenomena reach a crisis in the ninth month of pregnancy and especially in labor.

It may be contended that the development of proteinuria in labor is due to ischemia of the glomeruli due to arteriolar spasm, but since there is a distinct correlation between the degree of proteinuria and the stage of necrosis of the chorionic epithelium, we are more inclined to the view that toxic breakdown products of chorionic necrosis damage both the glomerular and tubular epithelium, producing proteinuria in labor in the same way it is produced by toxemia late in pregnancy.

While it cannot be denied that tissue damage and necrosis may result from long-continued vascular spasm, we are more impressed with the probability that these effects may be produced by intravascular formation of fibrin thrombi of thromboplastin origin, as described by Schneider (Schneider, C. L.: Am. J. Physiol. 149: 123, 1947) which block terminal arterioles.

DR. ROBERT A. ROSS, Chapel Hill, N. C.—One of the most available and consistent areas where blood vessels and circulation can be studied is in the eye. The changes in the retina associated with the pregnancy toxemias and vascular diseases complicated by pregnancy have long been known and appreciated. We have contended that these sometimes marked changes are not necessarily constant and we have insisted on a single observer commenting on the periodic changes and when possible having the findings photographed and made a part of the record. We have found the Department of Ophthalmology uniformly interested and helpful.

This group of workers, using a valuable new method of study with no preconceived idea, must make important observations. They wisely chose to study the bulbar conjunctival vascular bed in normal pregnancy and by a somewhat uncomfortable and tedious procedure they have contributed to our knowledge of circulation behavior during the full course of normal pregnancy. With this information and with the recorded clinical and postmortem data we can anticipate to some degree what their future findings in the toxemias of pregnancy might be. We know that there is no histopathologic lesion pathognomonic of toxemias of pregnancy. We do know, however, that hemorrhage into tissues and hyaline changes are usual findings in these patients. The authors have described the circulation changes on which these alterations in toxemia may be based. In our locality we are familiar with the nutritional anemias and the alternation of the albumin-globulin ratio and we do see the clinical complications of pregnancy toxemias. The blood volume and the blood count vary little in toxic and nontoxic patients. However, the blood proteins and the vascular phenomena do vary. By the expedient of regulating intake, fluids, minerals, vitamins, and output, we rarely see the fulminating toxic syndrome. By the simple use of fundoscopy we can note the more manifest circulatory changes, and by such studies as have been presented by the authors we can understand something more of the alterations even in normal pregnancy.

DR. LANDESMAN, New York, N. Y.—I would just like to make a few remarks to explain why we think this type of investigation may be of interest in a further understanding of the circulation in pregnancy. Retinal spasm is observed in relatively large arterioles and is seen in many severe toxemias. It is of considerable interest that these same changes of spasm occur in the terminal arterioles of the conjunctiva in the third trimester and during labor in normal pregnancy. This adds additional evidence to sub-

stantiate the general idea that toxemia of pregnancy is not a new process, but is a quantitative increase in certain findings which are present in a number of normal pregnancies. Bartholomew and Colvin and his other co-workers, as was brought out in the discussion, have indicated that there is albuminuria frequently during labor in normal pregnancy. This study may also shed some direct light on the peripheral circulation in pregnancy. The blood flow is considerably reduced by arteriolar spasm with slowing of the flow which is demonstrated by granularity and ischemia of the capillary bed. Exactly what occurs in the peripheral vascular bed of other tissues, and particularly in the liver, kidney, and uterus? These changes are still unknown and await future investigation. The relationship of essential hypertension to pregnancy has always been an intriguing one. The increased sensitivity to epinephrine in both these states suggests the possibility that similar biochemical factors are at work and that during pregnancy there is an added effect when essential hypertension is associated with normal pregnancy.

DR. DOUGLAS (Closing).—A very small aspect of this subject which we did not cover might be of some interest as it is somewhat provocative. Assali and his co-workers have very recently investigated the effects of one of the autonomic blocking drugs, namely, the tetraethylammonium chloride on the blood pressure in the toxemic patient and on the pregnancy. Interestingly enough, the patient who had pre-eclampsia late in the second trimester did not have any blood pressure response following the administration of this drug whereas this occurs in normal pregnancy. This difference does suggest, then, a shift from a possible neurogenic to a greater hormonal control of the vascular bed in toxemia.

TRIAL FORCEPS*

LOUIS H. DOUGLASS, M.D., AND D. FRANK KALTREIDER, M.D., BALTIMORE, MD.

(From the Department of Obstetrics and Gynecology, University Hospital)

THE attitude of most obstetricians toward the problem of contracted midplane and prolonged second stage of labor has undergone considerable change in the past few years. In the first place there is a more general acceptance of the fact that midplane and outlet contraction is a definite entity and it is rare that the statement is made today that if the head successfully negotiates the inlet, it will continue its passage through the birth canal with no further bony dystocia. Midplane difficulty is seen with sufficient frequency to warrant consideration on the part of every obstetrician. In addition we have learned by experience that it is not possible to predict in which individual case the midplane will offer little or no obstruction or when there will be a major difficulty, which can be overcome only at the expense of great risk to the infant and mother. The only definite answer to the question is a trial of labor at the midplane just as there is today, usually, a trial at the brim.

Everyone knows that midpelvic arrest may be due to a variety of causes, bony disproportion being only one, and that many of these are correctable, after which vaginal delivery is easy and safe. Therefore it would be poor obstetrics indeed to say that every patient with midpelvic arrest must be delivered abdominally or that all must be delivered from below.

From the literature and from personal conversation and communication it is quite apparent that many outstanding obstetricians are practicing "trial forceps" today, but it does not appear that anyone has documented his experience or results with this form of treatment. It is the purpose of this presentation to give a somewhat preliminary report of a small series of cases handled under this regime.

For the past several years the junior author has devoted considerable time to the x-ray study of the bony pelvis and the correlation of the findings with actual clinical results. Since July 1, 1947, he has reviewed the films of more than 2,000 pelvimetric studies, and, as a result of these studies and frequent consultations on various problems, we have developed in our clinic a philosophy toward several aspects of the over-all problem, one phase of which is that of the contracted midplane and outlet. It has become our practice to consider these as one problem rather than two, for it appears to us that one almost always accompanies the other and that there is practically no difference from the standpoint of treatment.

Material and Methods

Beginning Aug. 1, 1951, all service patients with suspect pelves were assigned to the junior author and all labors were conducted under his super-

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vision. He immediately instituted a regime of trial forceps in cases of mid- or low pelvic dystocia. This regime very briefly consists of the correction of abnormalities of position when this can be done easily and of *gentle* traction with the forceps. If further progress is not obtained, the forceps are removed and the patient delivered abdominally, unless the operation is contraindicated for some reason other than the forceps attempt.

For purposes of comparison the cases are divided into two periods, July 1, 1947, through July, 1951, and from Aug. 1, 1951, through April 15, 1952. Since the criteria of pelvic capacity most widely accepted in this country are those proposed by Mengert, we have used his method of determining the availability of the midpelvis and have selected 85 per cent of normal as the border line.

In Table I is shown the total number of pelvimetric studies, over 2,000, and the methods of delivery. While this is not a report of the entire clinic, it does include all cases of bony dystocia for it has been our policy to obtain pelvimetries in all cases of difficult or obstructed labor after delivery if it had not been done previously.

TABLE I. MATERIAL

	FIRST PERIOD		SECOND PERIOD	
No. of pelvimetries reviewed		1676		421
No. cesarean sections	235		40	
For midpelvic obstruction	8		2	
After trial forceps	1		2	
No. vertex vaginal deliveries		1189		346

In this presentation we are interested only in the midplane and therefore we have not listed the other indications for abdominal delivery. They do not differ from those found in comparable clinics elsewhere and would only confuse the issue if included here. It will be noted that in the first period there were 8 sections done for midplane obstruction, in only 1 of which had an attempt been made to deliver the patient by forceps, while in the second period in both of the sections done for this indication an attempt had been made. In this study we have also eliminated all cases of premature birth, multiple pregnancy, and abnormal lie, either breech or transverse. The remainder constitute the last item in this table.

Table II lists the cases according to Mengert's area, percentages being used instead of numbers for purpose of easier comparison. We apologize for the "indeterminable" group; however in these cases the films were not sufficiently clear to permit of accurate mensuration. This table is shown primarily to demonstrate that we are not dealing with a selected group of cases, nor is there any significant difference in the two groups.

TABLE II. DISTRIBUTION OF CASES ACCORDING TO MENGERT'S AREA OF MIDPELVIS

	FIRST PERIOD	SECOND PERIOD
85% and above	86%	85%
Below 85%	6.7%	7.5%
Indeterminable	7.3%	7.5%

Table III is also presented percentagewise and shows the incidence of difficult deliveries grouped according to Mengert's area. The phrase "difficult delivery" means a difficult mid- or low forceps or sufficient dystocia apparently to warrant abdominal delivery. While the type of delivery was copied verbatim from the chart, it is suspected that practically all of the difficult "low forceps" were actually midforceps deliveries.

TABLE III. INCIDENCE OF DIFFICULT DELIVERIES ACCORDING TO MENGERT'S AREA OF MIDPELVIS

	FIRST PERIOD	SECOND PERIOD
85% and over	9.5%	8.5%
Under 85%	35%	31%
Indeterminable	8.8%	10.2%
Total	11.2%	10.2%

The differences between the incidence of difficult delivery in those cases with an area above 85 per cent and those below this figure is considered to be statistically significant in both periods.

Table IV shows the duration of the second stage in this group of cases, and again there is shown a close correlation between the 2 periods. This table is primarily presented to demonstrate that there was no major change of policy in the second period other than the use of trial forceps in cases of midplane arrest.

TABLE IV. DURATION OF SECOND STAGE

	1ST PERIOD		2ND PERIOD	
MENGERT'S AREA	UNDER 2 HOURS	OVER 2 HOURS	UNDER 2 HOURS	OVER 2 HOURS
85% and over	84%	16%	83%	17%
Under 85%	75%	25%	71%	29%
Indeterminable	87%	13%	88%	12%
Total	84%	16%	82%	18%

The wisdom of allowing the second stage to continue for many hours is open to question. Evidence is accumulating that fetal mortality arises as this stage increases in length and, as a result of this study, we find ourselves more prone to interfere earlier.

In Table V we begin to show results to the babies and it is primarily in the interests of this very junior but very important patient that this method is being advocated. The risk to the mother does not appear to be greatly increased by subjecting her to abdominal delivery after attempts to complete the labor vaginally with forceps. This statement may prove to be unduly optimistic with more experience, but if the labor has been properly conducted, with attention to rest, fluid balance, and the prevention of infection, it is felt that the results should continue to be good. And the results to the baby appear to be equally good if gentleness and care are used. In this table it seems that infant results are not greatly influenced by the size of the pelvis, for the incidence of fetal injury is almost as great with a pelvis having an area of 85 per cent and over as with one below this point. While it is possible that there was an increased number of abdominal deliveries in the latter group, we do not feel that this alone was responsible. A bit later we will discuss this from the viewpoint of fetal size.

Table VI again presents results in the babies and is merely a condensation of the previous table. The fact that 18 infants were injured in a total of 141

TABLE V. INJURIES TO BABIES ACCOMPANYING SECTIONS AND DIFFICULT VAGINAL DELIVERIES

MENGERT'S AREA	NO. DELIVERIES		NO. INJURIES		INJURIES %	
	1ST PERIOD	2ND PERIOD	1ST PERIOD	2ND PERIOD	1ST PERIOD	2ND PERIOD
85% and over	102	26	12	0	11.8	0
Under 85%	31	9	4	0	12.9	0
Indeterminable	8	2	1	0	12.5	0
Total	141	37	17	0	12.0	0

deliveries in the first period and none in the second seems to mean that the change in policy contained some merit. We realize that the numbers are small in both periods and we do not expect to continue indefinitely with no fetal injuries. On the other hand, we hope we will never again reach an incidence of 12 per cent.

TABLE VI. INFANT RESULTS

	FIRST PERIOD	SECOND PERIOD
Living and well	124	37
Living with injury	5	0
Deaths	12	0

Table VII shows the causes of fetal injury and warrants some comment. The 2 cases of death attributed to second stage anoxia occurred in patients allowed to remain in this stage of labor for 3½ and 5½ hours, respectively.

TABLE VII. CAUSES OF FETAL INJURY AND DEATH

	FIRST PERIOD	SECOND PERIOD
Intracranial hemorrhage	9	0
Shoulder dystocia	6	0
Second stage anoxia	2	0

In neither instance did the cord prolapse nor did autopsy reveal any evidence of cerebral hemorrhage or other pathology. It is thought that the decreased size of the body of the uterus reduced the available oxygen supply to the point where it was incompatible with continued existence. This constitutes one of the dangers of a long second stage. We would also call attention to the 6 instances of shoulder dystocia. We have gained the impression from this study that a certain number of cases of midpelvic arrest are actually instances of inlet obstruction of the shoulders and that the difficulty is the result of a large baby rather than of a small pelvis. In any instance of failure of the forceps to produce descent easily, it becomes incumbent upon the operator to re-evaluate the fetal size. This is demonstrated in Table VIII where it is seen that both of the babies delivered abdominally after trial forceps weighed more than 4,000 grams. It is quite probable that had efforts at vaginal delivery been continued, serious shoulder dystocia would have been encountered.

TABLE VIII. SECTIONS FOR MIDPELVIC ARREST

	FIRST PERIOD		SECOND PERIOD	
Number done		2		
Following trial forceps	1		2	
Mengert's area 85% and over	6		1	
Mengert's area below 85%	2		1	
White	6		2	
Negro	2		0	
Weights of babies				
3,000 to 3,499 grams		2		0
3,500 to 3,999 grams		3		0
4,000 to 4,499 grams		3		1
5,000 grams and over				1

Of considerable interest to us was the fact that of the 10 sections done for midpelvic dystocia, 8 were in white patients. Since something more than one-half of our clinic is Negro and, since it is in this group that we see a large amount of our general pathology, it may be significant that this particular

type of dystocia occurred so infrequently. It is generally believed that inlet contraction is much more frequent in the Negro patient and it may well be that in this race the head will usually pass through the pelvis in the event the inlet can be negotiated.

It will be noted that we have not discussed fetal head size in this presentation. Our results of head measurements after delivery have been marked by a most distressing inconsistency and attempts at x-ray cephalometry have been extremely disappointing.

Comment

This study has convinced us that the midforceps operation, when always carried to conclusion, may be a very dangerous one for the infant, ranking second only to internal podalic version and breech extraction. On the other hand, many of these cases of midpelvic arrest may be capable of successful delivery with gentle traction and with a minimum of risk. If these gentle efforts fail, all attempts at vaginal delivery should be discontinued and resort had to the abdominal route. This does not appear to increase the risk to the mother while it is definitely less hazardous for the baby. It is true that the section rate may be slightly increased in theory, but it is doubtful if this will prove true in actual practice, for a certain number of patients delivered abdominally without trial forceps would be found to have easy vaginal deliveries when the attempt is made.

It should be emphasized that "trial forceps" is a method of delivery which should be undertaken only by a skilled obstetrician, and not by the general practitioner who has had no specialty training. This is also true of many obstetrical operations, not the least of which is a midforceps delivery itself. It is felt that this fact should not prevent its recommendation or its use.

Discussion

DR. W. K. STROTHER, Dallas, Texas.—Drs. Douglass and Kaltreider have introduced to us "Trial Forceps," a new obstetrical approach to some of our midplane problems. As brought out in the paper, there were comparatively few cases in which trial forceps were attempted followed by cesarean section. Since the number of trial forceps in this series is small, further experience with this technique, before a final evaluation can be made, is indicated.

Midpelvic arrest, due to causes other than cephalopelvic disproportion, whether as a result of small pelvis or large baby, should respond best to trial forceps. Arrest with disproportion at the midplane yields little to gentle traction.

Living with him, we too have adopted Mengert's idea of evaluating pelvic capacity. With 85 per cent as the dividing line, it has proved to be very satisfactory in studying cephalopelvic relationship. As in the study of Dr. Douglass, we have found that most of the difficult forceps and cesarean section operations were on patients whose measurements were below that figure. It should be borne in mind, however, that x-ray personnel and measurements are subject to human error, and pelvimetry should be used only as an adjunct to astute clinical judgment. The force of labor and moldability of the fetal head comprise the unpredictable factors in any given case.

It is obvious from Dr. Douglass' figures that cases supervised by one individual fare better than those of a heterogeneous staff. This is true in Mengert's series, which consists of 2,447 deliveries in the year 1951. In this group there were 63 cases of pelvic contraction; 48 were delivered by cesarean section and 15 by necessary forceps. The cause

of death was not given for the one fetal fatality in the cesarean section group. There were no trial forceps in this series.

During the same year at Baylor Hospital, with a general staff, there were 5,824 deliveries with a total of 279 cesarean sections. Indication for 96 of these was listed as cephalopelvic disproportion. Of this last group, 8 had attempted delivery by forceps and were subsequently delivered abdominally, two by extraperitoneal section. As cesarean section had not been contemplated in this group, they were listed as failed forceps. There was one fetal death due to cerebral hemorrhage in this group of 8. The maternal morbidity was practically nil. If the principle of restraint, as suggested by the essayist, had been applied to this group, I feel certain the operation would have had a more satisfactory conclusion for both mother and baby. The use of antibiotics and blood does not obviate the necessity for good surgical practices.

The success of the procedure described must depend on several things. How much is "gentle"? It certainly will vary with each individual, for have we not all scrubbed in with a resident to aid in a forceps delivery and found he was just not applying quite enough force? One of the younger members of our staff was asked for his idea of gentle traction. His facetious reply was, "It is that force that could be applied to the forceps without moving the delivery table with the wheels of the table unlocked." Definitely, as stressed by the essayist, this is an operation for the few, for certainly its success is based on judgment and experience. Other things by which we may be influenced are: length of time the patient has been in labor, ruptured membranes and length of time ruptured, and the condition of mother and baby at time of contemplated delivery.

Certainly trial forceps offers much in the prevention of a long second stage. The trauma attendant to a prolonged second stage is of considerable importance to the welfare of the infant. The old teaching that patients should be delivered after two hours of full dilatation of the cervix may have its merit. We have all seen the bad results of procrastination in patients with cervices fully dilated.

Antibiotics, fluids, blood, and anesthesia have gone a long way in helping us out of trouble and protecting the patient. They will not, however, protect the patient against irreparable soft tissue damage, even though we get a good baby. The midpelvic forceps operation deserves the greatest respect, particularly when the patient is to be seen by us through the years that follow. We all have some patients we hate to see come back to our offices!

The procedure described by Drs. Douglass and Kaltreider has its merit. As stated by them, this operation should be undertaken only by skilled obstetricians, and they with the temerity to back out and deliver the woman abdominally if the force required to deliver her vaginally is other than gentle.

DR. JAMES L. REYCRAFT, Cleveland, Ohio.—The use of trial forceps is a subject of provocative nature and we should not be hasty in our approval or disapproval of its merits. In the hands of an experienced operator it may be justified, in this day of utilization of the antibiotics. We are prone to associate its use with the cases we have seen all too often of attempted deliveries which were unsuccessful from below, and the patients were sectioned with disastrous results. In the practice of conservative obstetrics there is seldom occasion to deliver a patient by section *after* forceps delivery has been attempted.

We have been in close contact with an experienced and capable roentgenologist who affirms that pelvic dystocia involves the inlet in 90 per cent of our cases. However, this paper concerns the relatively small number of instances in which the midpelvis and outlet are involved.

Within the past month I had occasion to examine a patient who had been delivered of her first child by cesarean section by an obstetrician in our city. Routine examination showed the scar of an episiotomy and vaginal as well as cervical lacerations. Fortunately, she had made a good recovery, but this was certainly not an instance of the use of gentle trial, as the essayist has advocated.

In the University Hospitals of Cleveland the procedure proposed has seldom been utilized. However, in the past three decades a very high percentage were delivered by low or midforceps as a means of expediting the delivery, always under adequate anesthesia.

We all agree that midpelvic arrest is due to: (1) disproportion between the passage and the passenger, (2) a malposition of the head, or (3) uterine inertia. The ability of the head to mold must also be considered. With the membranes ruptured and the cervix fully dilated for at least two hours, and with the head in the pelvis, we do not hesitate to correct a posterior position very gently by the Bill maneuver, and proceed with the delivery.

Mengert has given us an ingenious method of estimating the capacity of the pelvis by x-ray at the various levels. As he says, the method of determining the measurements is irrelevant. He has standardized the measurements percentagewise and, after much study, has reached the conclusion that to be adequate the percentage should be at least 85 per cent of the accepted normal. This sounds like a reasonable standard. Since accurate measurement of the size of the fetal head is very difficult, there may be a disproportion, even though the pelvis is approximately normal in size, especially if there is a malposition of the presenting part.

In analyzing the studies presented today it seems almost incredible that there were absolutely no fetal injuries in the second period, as noted in Tables V and VI. One would assume that the forces of labor alone would have caused the evidence of occasional injury through trauma or anoxia. It points up the fact that the number of cases was not great enough to justify the conclusions implied.

The fetal size is of paramount importance and before any attempt at forceps delivery is made it should be ascertained, as accurately as possible, whether there is likely to be difficulty in delivering the shoulders. We all see instances in which the shoulders are so large that they do not enter the inlet, and consequently the head does not descend in its normal fashion.

As I said at the beginning of my remarks, I think this subject is highly provocative, and time alone will tell whether it will become a part of our armamentarium.

DR. J. BAY JACOBS, Washington, D. C.—I discuss this paper because of my interest and experience in x-ray pelvimetry, which dates back as far as 1928. I have found that the most difficult thing for me to do is to evaluate midpelvic contraction.

I can readily evaluate an inlet, detect its contour, and determine its various measurements, as well as the anteroposterior diameter of the midpelvis and the posterior sagittal diameter. But I have never been convinced that an accurate appraisal of the midpelvis is possible in the average case since the ischial spines are seldom clearly visible. In such instances, the roentgenologist usually sketches them in, and although I have much respect for the experienced roentgenologist, I have little regard for such determinations. Then again, there are other physical characteristics involved in the technique of pelvimetric roentgenography that affect accuracy in measuring the interspinous diameter. For that reason I have insufficient confidence in the whole procedure. I believe that there is good sense to the theory evolved by Mengert, and perhaps we could be guided by his index if we were able to measure the interspinous diameter more perfectly.

As far as Dr. Douglass is concerned, I think he is very practical and has presented a subject that should impress all of us. When the average obstetrician attempts delivery from below with forceps he is determined to complete the delivery in that manner. Dr. Douglass lets us know that it is all right to change our minds and course of procedure. Contrary to what one may think, there is no embarrassment attached to a change in decision, and perhaps it should be done more frequently. Seldom would it be necessary to make such a change if it were possible to appraise a midpelvis more accurately.

I have always felt that in the majority of cases midpelvic contraction is associated with outlet contraction. It was pleasing to note that Dr. Douglass has made a similar observation. It is difficult to conceive of a pelvis that would suddenly dip in the middle and widen at the outlet. The logical thing to expect would be a general contraction extending progressively downward from the inlet to the outlet, and I believe that his condition usually obtains,

although in the very rare case midpelvic contraction may exist independent of outlet contraction. Dr. Douglass' statistics seem to confirm this view.

In handling the contracted outlet, I have always found it most feasible to appraise the arch and the bi-ischial diameter clinically, and to measure the posterior sagittal on the lateral pelvic roentgenogram where it can be done quite accurately, and then follow the standard advocated by Thoms for outlet appraisal, considering 15.5 cm. as the minimal normal total of transverse outlet and posterior sagittal, for delivery of a head of average size.

In the patient with borderline midpelvis and outlet, when the intention is to deliver from below, I prefer to perform a mediolateral episiotomy and regulated suprafundal pressure rather than to use forceps. This combination usually produces good results. On the whole I think that one of the most difficult and obscure problems we have to deal with is midpelvic and outlet contraction, and Dr. Douglass has presented us with something worth our consideration.

DR. WILLIS E. BROWN, Little Rock, Ark.—One may view the human pelvis as an anatomist or as a functionalist. The anatomist is interested in the size, shape, measurement, etc., while the functionalist is interested in whether the pelvis will accommodate a given child. It matters little to me as a clinician what the size, shape, measurement, or percentage capacity of a pelvis may be, if it will not accommodate the head of the child in the uterus at this time. We cannot predict by measuring the pelvis the position, size, or moldability of the fetal head, or the strength of the uterine contractions, all of which are variable and come to bear upon the outcome of labor.

Consequently, we have long lost any embarrassment at being unable to predict the outcome of labor. Before trial labor was introduced, we frequently found ourselves recommending an elective section only to have the patient deliver while preparations were being made. We believe that trial forceps fall in the same category as trial labor. I was taught, and I am sure that most of you were taught, that once you put on the blades something had to come out. It was a "challenge" between you and the pelvis. If we will drop the "challenge" in forceps and adopt the "trial" of forceps, I am sure many infants will be salvaged and many sections avoided.

We have adopted "trial forceps" at the University of Arkansas and I can assure you that we have been very pleased. In many patients who appeared obviously to need a section because of an arrested head at the midpelvis, a slight rotation and trial forceps resulted in successful vaginal delivery. In others in whom there seemed to be no insurmountable obstruction, the forceps failed to establish favorable accommodation and the abdomen was opened. I think we now are in a position to add "trial forceps" to "trial labor," but don't make it a *challenge.*

DR. DOUGLASS (Closing).—As I have stated, the number of cases is small and the conclusions reached may not be entirely accurate. On the other hand, we believe that the theory of "trial forceps" is a sound one and that its acceptance and use will materially reduce injury to the baby. At the same time it is conceivable that the incidence of abdominal delivery will be reduced, in that in many cases which might otherwise come to section there will be easy midforceps deliveries after abnormalities of position have been corrected.

We agree with Dr. Jacobs that it is rare indeed to see a patient with a contraction of the midpelvis who does not also have an outlet contraction.

Finally, let me say that it is a most comforting thought when sitting down to do a midforceps operation that one is not irrevocably committed to vaginal delivery.

THE VALUE OF THE LATERAL PELVIC ROENTGENOGRAM AS AN INDEX OF FETAL MATURITY AND TYPE OF MATERNAL PELVIS*

J. Bay Jacobs, M.D., F.A.C.S.,** Washington, D. C.

THE routine correlation of pelvimetric determinations with clinical evaluation, combined with a personally conducted labor and delivery, affords the obstetrician a feeling of satisfaction, and results in the utmost consideration to the patient with the borderline pelvis.

In an article entitled "Further Improvement in Pelvimetric Roentgenography," published in the July, 1936, issue of the American Journal of Obstetrics and Gynecology, I[1] was first to describe the technique of lateral pelvic roentgenography in the standing posture. The ideal time for such study is as late in pregnancy as possible and for that reason I have always designated the end of the thirty-eighth week as the most practical time. Should the patient start in labor before this time, the picture can readily be taken then. Frequently, labor does not ensue until after 40 weeks.

The main advantage of the standing posture is that it favors engagement of the presenting part and affords a good appraisal of cephalopelvic relationship. In the recumbent posture the presenting part, unless well engaged, has a tendency to bob away from the inlet and for that reason is more subject to distortion and error of measurement, roentgenographically. Mensuration and impressions thus obtained are less reliable.

On previous occasions,[2, 3] I have referred to the simplicity and accuracy of this method, and enumerated its many advantages. I have also devised film scales which simplify the procedure and save time and expense.[3] The technique has received wide recognition, and the original idea of the standing posture is generally credited to the name of Thoms,[4] since he has probably given it most publicity.

Since 1929, when I first became interested, I have felt that pelvimetric roentgenography is our greatest adjunct in obstetrics. Measurements obtained by anteroposterior techniques commonly used, as I[2] have expressed previously, are subject to some degree of error. However, this view, by the various techniques proposed, is essential for classification of pelves, since it clearly outlines the contour of the plane of the superior strait and affords fairly reliable measurement of the transverse diameter of the inlet.

Architectural features of the pelvis and fetal skull are more clearly demonstrable and reliable measurements are more easily obtained in the lateral view. For these reasons and several others, I have requested only lateral pelvic roentgenograms on patients with borderline pelves, both in private practice and in

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the clinics of the Health Department of the District of Columbia. I have always felt that classification of pelves is desirable for teaching and purposes of description, but is not essential for actual management.

I am convinced that by obtaining a lateral pelvic roentgenogram of every primipara with a diagonal conjugate diameter of 11.5 cm. or less, and of every multipara with a diagonal conjugate of 11 cm. or less, no case of borderline or contracted pelvis will escape recognition. It is presumed, of course, that at the time of selection or designation of these cases for roentgenography, the outlet is adequately appraised from the clinical point of view.

In the routine interpretation of several thousand lateral pelvic roentgenograms, certain observations and findings have impressed me. Some of these, relating to prognostication, management of labor and outcome, were presented before this Association on a previous occasion.[5] In that study my attention was directed particularly to the true conjugate diameter, and a method of appraising the individual borderline pelvis, from a practical point of view.

During the many years that I have been observing lateral pelvic roentgenograms taken in the standing posture, the repeated occurrence of certain other factors has impressed me. In this presentation, I wish to direct attention to two of them.

First is the fact that in most instances the biparietal diameter applies itself or engages in the true conjugate. This occurs so commonly that it caused me to believe that when any other diameter of the fetal skull applies itself to the true conjugate, an unusual type of inlet, such as is seen in the anthropoid pelvis, must be the governing factor.

The second impression that I acquired, and which I desire to direct attention to, is that one should be able to determine the degree of fetal maturity from the size of the biparietal diameter, accurately measured. For this purpose, I consider my technique of lateral pelvic roentgenography in the standing posture as simple, inexpensive, and reliable.

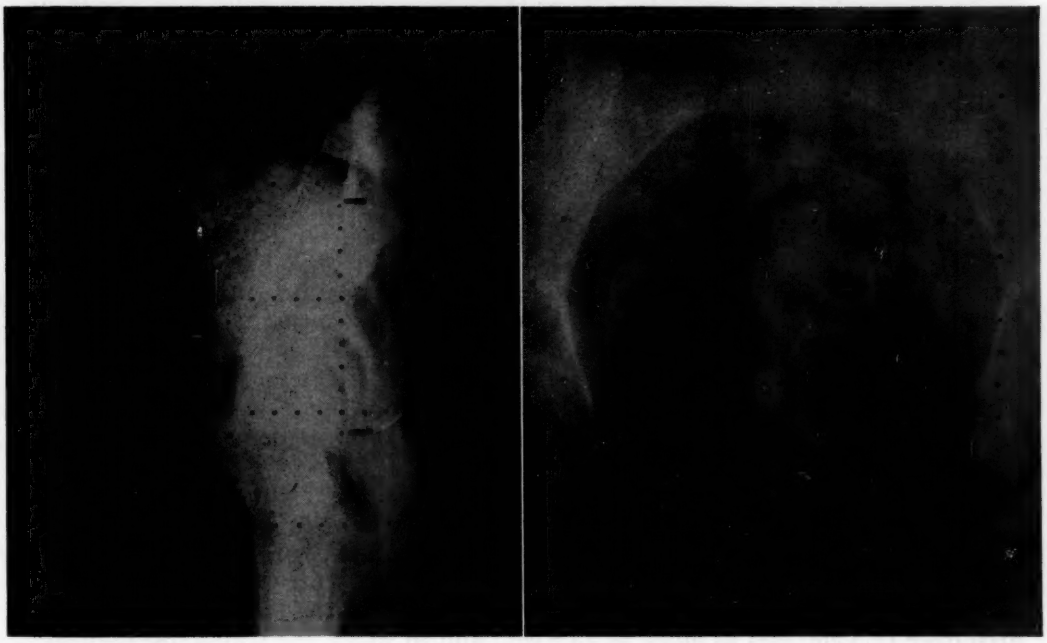
Although I had never gathered statistics on these points, I have for many years utilized this information in determining the maturity of a baby, prior to the induction of labor or the performance of elective cesarean section. I do not recall any instance where I had been misled.

Material and Methods

For the purpose of this study, I reviewed my interpretation of 1,691 lateral pelvimetric films, selected at random as time and clerical assistance would permit. In addition, for the purpose of noting whether inlet contour affected the position of the head as seen in the lateral pelvic roentgenogram, I reviewed the films of 169 patients in whom both a lateral and anteroposterior view were taken. Therefore, the combined number of cases reviewed was 1,860. The series of 1,691 cases was taken from my clinics at the Health Department of the District of Columbia, where I had been studying borderline pelves by lateral pelvic roentgenography in the standing posture for over sixteen years. The smaller series was picked at random from the files of Drs. Groover, Christie, and Merritt, a group of skilled roentgenologists who use my technique of lateral pelvic roentgenography in the standing posture, and the Thoms technique for the inlet view, in all cases.

Although Negro patients are in the great majority in the Health Department clinics, I am ignoring the question of color in this study because it was noted that color plays no part in the items that I am about to discuss.

As previously stated, my intention was to determine first the frequency of biparietal application to the true conjugate diameter. This was noted in 1,088 of the clinic cases while some other diameter of the fetal skull presented in 603 cases. In the private patient group, the biparietal diameter presented in the true conjugate in 109 cases, while some other cephalic diameter presented in 60 cases. Thus it is seen that the incidence is almost identical in both groups. In other words, the biparietal diameter presents itself for accurate measurement on the lateral view in the standing posture, in two out of three cases. Note that the standing posture is emphasized because, in the recumbent or any other posture, physical conditions are altered and resulting calculations and impressions would be less reliable. For instance, it is commonly noted that a head which engages with the biparietal diameter in the true conjugate frequently shifts into some other diameter of the pelvis merely by slight altering of the patient's attitude, such as placing her in the semirecumbent posture, as when an anteroposterior view of the inlet is obtained (Fig. 1).



A. *B.*

Fig. 1.—*A*, Perfectly aligned lateral view of the pelvis in the standing posture. The head is well engaged, with the biparietal diameter in the anteroposterior of the pelvis. The occiput and chin are also clearly visible. Arrow points to upper border of symphysis. The occiput, parietal eminences, and chin are also marked. In this view the length of the true conjugate is measured most accurately.

B, Anteroposterior view of same pelvis, taken by the method of Thoms. This pelvis is ample.

Both pictures were taken within a few minutes of each other. Note that the position of the head has shifted, and the biparietal diameter is no longer in the true conjugate. In this view the transverse diameter of the inlet is measured most accurately.

Does the Contour of Inlet (Type Pelvis) Influence Manner of Engagement of Fetal Skull?

As previously stressed, there is a tendency for the head to engage with the biparietal diameter in the true conjugate in two out of three cases. This rela-

tionship exists, regardless of color or parity. Because of the constant frequency of biparietal engagement, it was my impression that the contour of the inlet might be a determining factor. I felt that, when any other type of engagement obtained, it was because the long axis of the skull applied itself to the most available long diameter of the maternal pelvis, or that engagement was influenced by the contour or type of pelvic inlet.

Since my impressions were formed almost entirely by the interpretation of lateral pelvic roentgenograms, I expected to confirm these ideas by noting the inlet contour as obtained perfectly in the properly taken anteroposterior film. Because of the time element and the difficulty involved in getting clinic patients to return weeks, months, or years after delivery, I decided to review a series of readily accessible films of private patients in which both anteroposterior and lateral views were taken before delivery. At first 60 cases in which the biparietal diameter did not engage in the true conjugate were selected at random. The measurement of the true conjugate diameter was taken from the lateral film, for here it is obtained with greatest precision. The transverse diameter of the inlet was measured on the anteroposterior film, for here it could be obtained more precisely than any other inlet diameter; and of course it could not be observed on a lateral film. Thus the principal measurements and contour of the inlet were established, and the position of the head in relation to these inlet diameters was observed.

It was noted that in 35 instances the occiput was directed toward the symphysis and in 4 cases the occiput was directed toward the sacral promontory, while in the remaining 21 cases the longitudinal suture applied itself to one of the oblique diameters of the inlet.

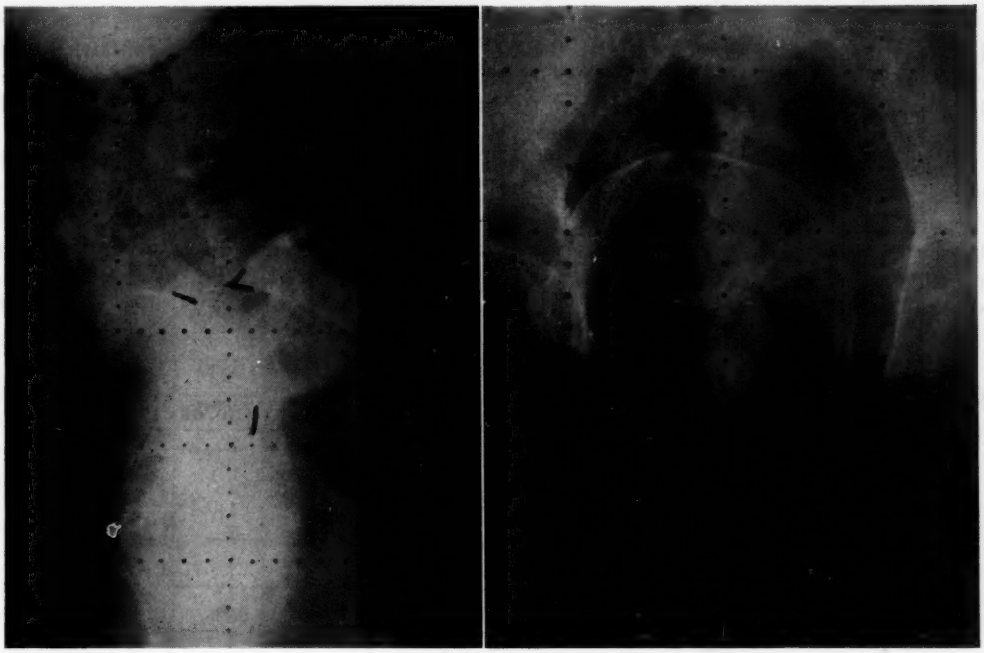
The shape of the inlet and the relationship between the length of the true conjugate diameter with that of the transverse diameter of the inlet seemed to have no governing influence on the position that the head occupied. In numerous instances the head engaged with the longitudinal suture in the anteroposterior diameter of the inlet even though the true conjugate and transverse diameters were of typical gynecoid relationship. In many of the cases where the longitudinal suture was in one of the oblique diameters, it was noted that the transverse diameter of the inlet was below average.

In 15 out of this series of 60 cases, the transverse diameter of the inlet was 12 cm. or less.

After making the observations on these 60 cases, I thought it would be well to analyze in a similar manner the 109 sets of films in which the biparietal diameter presented. To my surprise, the relationship of true conjugate to transverse diameter of the inlet was almost identical with that in the 60 cases just referred to. There were many instances in which the true conjugate measured over 12.5 cm. and as much as 13.8 cm., and in which the transverse diameter of the inlet was relatively reduced. It was surprising to note that with such contour of the inlet the biparietal diameter presented in the true conjugate so frequently (Fig. 2). In this series of 109 cases (biparietal presenting) there were 26 in which the transverse inlet measured 12 cm. or less. This is quite comparable to the incidence in the 60 cases previously referred to. Thus it is seen that decrease in size of the transverse diameter of the inlet does not seem to affect the manner of engagement of the fetal skull. In like manner, the contour of the inlet, unless abnormal to an extreme degree, does not seem to disturb the two-to-one relationship of biparietal diameter to other presenting diameters of the head. Many inlets were very large in both dimensions, but in spite of that fact the same incidence as far as engagement is concerned, existed. I have been wondering whether the dimensions of the fetus in its attitude of universal flexion, as well as the dimensions of the uterus at term might not

be a factor in influencing engagement of the biparietal diameter in the true conjugate. When we realize that the anteroposterior dimension of the flexed fetal body is probably greater than the lateral dimension and that the lateral dimension of the uterus is greater than the anteroposterior, it is possible that, in the standing posture at least, these factors may play a part. If there is any merit to this theory, the fetal small parts would most frequently be located on one side of the mother and the back on the other as would be the occiput. The biparietal diameter would then be in the true conjugate.

From these observations I conclude that, unless some definitely abnormal contour of the inlet obtains, the manner of engagement of the fetal skull is not affected, and the two-to-one relationship of biparietal to other presenting cephalic diameters, is not altered.



A. *B.*

Fig. 2.—*A*, The biparietal diameter is in the true conjugate, as shown in the lateral roentgenogram in the standing posture, in spite of the fact that the patient has (*B*) an anthropoid inlet with a transverse diameter of only 11 cm.

On *A*, the parietal eminences, occiput, and sacral promontory are marked.

The Biparietal Diameter as an Index of Fetal Maturity

To have a most effective application, x-ray pelvimetry necessarily includes consideration of cephalic as well as pelvic measurements. Some authors have concentrated upon methods of fetal cephalometry.

Clifford[6] was interested in mensuration of the fetal skull in order to determine the maturity of the fetus or its viability.

McElin and his co-workers[7] experimented with the method of Cave, by which diameters of the fetal skull are obtained roentgenographically. Although these authors comment favorably on the technique and theory of Cave,[8] I am not influenced because pictures are taken in the recumbent posture. In this position almost any diameter of the fetal skull might appear in projection upon the x-ray film. In many cases, it is difficult to say just what diameter appears,

in which event there would be no standard that one could follow to determine fetal maturity. The same criticism would apply to the methods advocated by many other authors.

Scammon and Calkins[9] developed a graph to show the age of the fetus in weeks depending upon the size of the occipitofrontal diameter.

Roentgenologists generally attempt to determine maturity of a fetus in utero by noting appearance of the long bones and the development of certain epiphyses. This is recognized as more or less standard procedure.

Recently, Christie and his group[10] studied the osseous development of the fetus in 100 pregnant women, paying particular attention to the development of ossification centers of the distal epiphysis of the femur and proximal epiphysis of the tibia. Thus they attempt to determine the maturity of the fetus. Their determinations appear worthy of consideration.

I have been interested in determining fetal maturity by noting the size of the biparietal diameter in utero. This diameter is most easily identified, and can readily be differentiated from confusing diameters such as would present themselves upon slight rotation of a head, as well as from other recognized diameters of the fetal skull.

As repeatedly stated, the biparietal diameter presents in two-thirds of all cases studied by my technique of lateral pelvic roentgenography.

In 761 of my clinic cases it was readily possible to obtain the date of delivery as well as the weight of the fetus at birth. Time and other circumstances prevented me from obtaining such information in many of the other cases that were available. All were vertex presentations, with spontaneous onset of labor.

TABLE I. PRENATAL BIPARIETAL DIAMETER. STUDY OF 761 CASES (JABOBS)

BIPARIETAL DIAMETER	FREQUENCY (NO. OF CASES)
7.0	2
7.4	2
7.5	3
7.6	1
7.7	7
7.8	7
7.9	1
8.0	83
8.1	1
8.2	40
8.3	33
8.4	42
8.5	78
8.6	44
8.7	60
8.8	49
8.9	21
9.0	157
9.1	9
9.2	47
9.3	16
9.4	18
9.5	19
9.6	2
9.7	8
9.8	2
10.0	6
10.2	2
10.8	1

Table I shows the number of cases for each length of biparietal diameter at the time of x-ray. It so happens that relatively few patients were referred by my clinical assistants for x-ray pelvimetry previous to the time that the fetus had attained a biparietal diameter of 8 cm. It is noted that in 83 patients the biparietal diameter measured 8 cm. and in 40 cases it measured 8.2 cm., and from this point on the incidence is relatively large for each measurement, becoming greatest at 9 cm. when the number of cases was 157. After 9.2 cm., the frequency of cases diminishes so that there are very few recorded at 9.6 cm. and beyond.

In plotting the individual cases for the purpose of formulating a graph, it is readily seen that the bulk of material that can be utilized to show trends exists in the cases that have biparietal diameters from 8 to 9.2 cm.

Fig. 3 is the result of plotting 761 cases in which the biparietal diameter was determined by the technique described, the number of days known between the date of x-ray and delivery, and the birth weight.

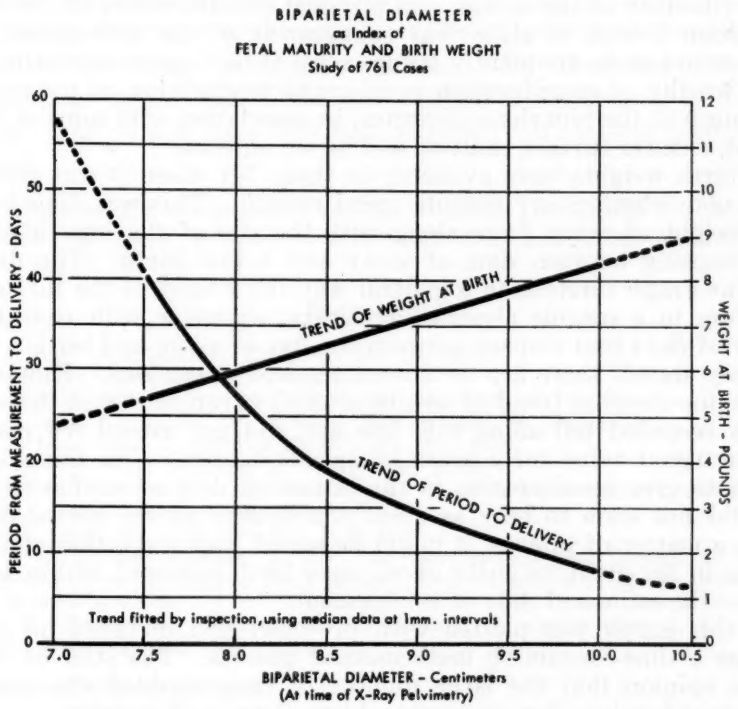


Fig. 3.—Assuming that the length of the biparietal diameter in utero is 9 cm., read upward to "trend of period to delivery" line, and then to the left, noting that period from time of measurement to delivery will be about 13 days.

Reading upward to the line marked "trend of weight at birth," and then to the right, reveals that the baby might be expected to weigh about 7.1 pounds at birth (about 13 days after date of x-ray). Such information may be readily obtained from the graph in any case where the length of the biparietal diameter is known in centimeters and fractions thereof.

It is noted that reference to the line marked *Trend of Period to Delivery* gives the approximate number of days that should intervene between the date of x-ray and delivery, for any biparietal measurement. Thus it is seen that when the biparietal diameter measures 8 cm. labor might be expected to ensue in the neighborhood of 28 days from the date of x-ray. In like manner, when the biparietal diameter measures 9 cm., one might expect labor to ensue in about 13 days. Although the time to delivery may vary widely in a few cases, it was

found that two-thirds of them fell within limits of from 7 to 10 days plus or minus the trend value.

In my experience I have encountered occasional cases where the biparietal diameter appeared unusually large, but upon investigation I learned that the father of the baby had an unusually large head. Such a fetus will weigh less at birth, in proportion to the length of the biparietal diameter, than the average.

Although a careful analysis of the whole series of cases, by experts, results in the definite trend shown, a word of caution is indicated at this point. One must realize that graphs express trends or generalities and that exceptions to the rule are not uncommon. In spite of the fact that this curve conforms to the impressions that I have always entertained, I wish to direct attention to the necessary practical considerations that must be associated with its application. For instance, if one is about to induce labor or determine a date for elective cesarean section, he can usually decide upon maturity by noting such factors as the size of the uterus, the amount of amniotic fluid, the estimated date of confinement, the birth weight of previous children, engagement of the presenting part, irritability of the uterus, and physical characteristics of the cervix. In this connection I wish to state that engagement of the presenting part in a multipara occurs more frequently before term than is generally believed. This is an item worthy of consideration previous to termination of pregnancy.

The length of the biparietal diameter, in association with some of the factors enumerated, ensures further caution, and better outcome.

Since birth weights were available in these 761 cases, it was considered of interest to note whether any definite trend existed. This was done by plotting the birth weight of every fetus along with the size of the biparietal diameter and days elapsing between date of x-ray and actual birth. The definite line shown on the graph foretells in a general way the weight of the infant at birth, corresponding to a specific observed biparietal diameter with consideration to the number of days that elapsed between the day of x-ray and birth. Of course, as previously stated, there are occasional marked exceptions. However, in regard to the line showing trend of weight at birth it can be stated that two-thirds of all cases recorded fell along this line and did not exceed 0.9 pound above or below the trend value for a given biparietal diameter. In this study it was decided not to give consideration to the estimated date of confinement because that fact did not seem to bear as great significance as the actual date of delivery. As a matter of interest it might be stated that inspection of the records showed that in the great majority of all cases birth occurred within 10 days before or after the estimated date of confinement.

Since this graph was plotted with precision and included all of the 761 cases, it was a time-consuming mathematical process. The staff of experts expressed the opinion that the large number of cases enabled the establishment of reliable trend values for estimating birth dates and weights.

Summary

A few of the practical principles of x-ray pelvimetry have been emphasized, with particular attention to the merits of the lateral roentgenogram and the standing posture.

The purpose of the study was to determine whether the biparietal diameter lends itself to accurate mensuration often enough and whether its length as an index of maturity is reliable enough to be of practical value in making the important decisions which so commonly confront the obstetrician.

Since it was my impression that the biparietal diameter entered the true conjugate so commonly, the general belief was that failure to do so might indi-

cate an atypical pelvic contour. This, however, is not the case, since the same type and size of superior strait was found in two samples of cases—those in which the biparietal diameter entered the true conjugate and those in which any other cephalic diameter engaged in the true conjugate diameter.

Conclusions

1. The biparietal diameter can be accurately measured in two-thirds of all vertex presentations, by the author's technique of lateral pelvic roentgenography in the standing posture.

2. Analysis of 761 roentgenograms in which the biparietal diameter was measured convinces me that my impression of the practical application of this principle is correct.

3. The graph developed can be used to forecast with considerable certainty both fetal maturity and weight at birth.

4. Although reference to the graph will be of great assistance in the management of certain cases, its application should be correlated with the usual physical findings in the individual case. This is important, because graphs show trends; they do not make decisions, especially in the less common unusual circumstance.

Acknowledgment for technical skill and knowledge in plotting the 761 individual cases that compromise this graph, is given to Douglas N. West and L. M. Abbe of the United States Public Health Service.

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Washington Medical Building

Discussion

DR. ALFRED L. POTTER, Providence, R. I.—Our experience at Providence Lying-In Hospital has been with the precision stereoscope. A request for consultation is often an invitation to "look at a pelvis with me," to LOOK at a pelvis and its fetal contents, to see and almost touch the virtual image of the whole pelvis, inlet, midpelvis, and outlet in their true relationships and proportions.

In the attempt to develop a simple, useful, and economical method of x-ray examination, in 1936 Dr. Jacobs showed the usefulness of a single lateral view of the pelvis at term or even in labor with the patient standing. We found this erect picture to be a great improvement in bringing the presenting part into the inlet. We combined this with the two stereoscopic views of the inlet and the anteroposterior view in a complete study of the pelvis. If lack of technical equipment or skill, or financial considerations limit the study to one single film, the erect lateral view at term is the most valuable. It gives the fetal-

maternal relationship, progress in engagement or descent, and, as now shown, an accurate measure of the size and maturity of the fetus.

Dr. Jacobs reminds us that any variant of the midpelvis may coexist with any type of inlet. The opposite also holds true. A pelvis with a normal lateral conformation may have close ischial spines or converging side walls. The lateral view can be used for classification only by inference, using as clues the position of the head, station in the pelvis, contour of the sciatic notches, number of sacral segments, etc. If the head is transversely engaged we probably have a "favorable" pelvis.

It is trite to quote Bumm's words that "the best pelvimeter is the baby's skull." All of us use this pelvimeter in observing the ability of the head to engage at term or in labor. Clinical experience affords such a functional appraisal of the inlet without danger. However, the contracted midpelvis does not lend itself as safely to study by Bumm's pelvimeter alone. The lateral view alone cannot foretell the capacity of such a midpelvis, for the inlet and midpelvis do not necessarily correspond in having good architectural features.

Dr. Jacobs statistically confirms that in two of three cases the biparietal diameter enters the inlet in the sagittal plane in the midline, and that this is the usual normal mechanism. The other third which do not so engage he regards as possibly of an unusual type or size. The anthropoid pelvis, which makes up about one-fifth of most series, seems to me to be a reasonably usual normal variant, and offers no difficulty except that if such shape requires any mechanism, engagement and descent will be in the sagittal plane and an occipitoposterior may persist to the outlet. By a lateral view alone such a normal anthropoid pelvis will be classed with the abnormal; and worse, the good inlet with contracted midpelvis will be overlooked. Dr. Jacobs points out that a definite type or size of inlet is not necessarily associated with any one position of the head. He emphasizes that many factors influence its position at the inlet not demonstrable by x-ray, such as shape of the uterus, strength and length of supporting structures, and amount of amnoitic fluid or freedom of the fetus.

Cephalometry has been disappointing. We are inclined to place little reliance on prognosis based on volumetric comparisons of fetal head and pelvic capacity. Fortunately, variations in the shape of babies' heads is not as important as variations in the shape of their mothers' solid and unyielding pelves. The head can flex and incline, and can change its diameters by molding. Of all the diameters the biparietal seems least changed in labor. Whether the baby comes of long- or round-headed stock matters little; the head is hinged and the long occipitomental diameter is of little clinical significance, although it alters volumetric comparisons greatly. The biparietal offers the most constant single criterion for head size and is also the diameter we are concerned with in all stages of the head's progress through the pelvis. Any other is irrelevant. And now Dr. Jacobs shows us that we can usually determine this diameter easily and accurately, and by his graphs can use it to approximate the length of gestation and maturity of the fetus.

Some critic will ask what we are to do when the head is not engaged transversely. If the head is floating, no present method of pelvimetry can be accurate. If the head is in the inlet but not suitable for lateral exposure, I suggest that this critic get a precision stereoscope.

Dr. Jacobs realizes that all babies are not born with the same sized heads. In any cosmopolitan American population subject to varied racial, familial, and nutritional influences, the size of the baby often surprises us. In an attempt to get an idea of the paternal influence I once asked my patients what sized hats and shoes their husbands wore. They seldom knew, and such fruitless conversation resulted ended by my giving up the idea. In using his graphs Dr. Jacobs warns that we are to take into consideration all such bits of information as he enumerates, and not use the graphs blindly.

The present contribution will prove as valuable in electing the proper date to repeat a section or in calming the anxiety of a patient overdue by date as was his earlier suggestion, of which we are well reminded, that the lateral erect view of the pelvis is the most valuable single x-ray study available to any one, anywhere, who has a perforated metal ruler and an x-ray machine.

DR. L. MARSHALL HARRIS, Newport, R. I.—The opportunity to discuss Dr. Jacobs' informative and practical presentation has revealed a very substantial bibliography of the members of this Association who have contributed significantly to roentgen pelvimetry since the beginning of x-ray pelvimetry in 1896 with the work of Varnier, Budin, and others. Dr. Jacobs' paper, to my personal knowledge, represents an exhaustive study and conscientious investigation over a period of twenty years on the subject of roentgenographic pelvimetry, as it applies to the technique and interpretation of roentgen studies of the female pelvis, more recently the technique and interpretation of cephalometry.

In addition to the outstanding contribution in this field by numerous Fellows of this Association, the work of Thoms of Yale, which dates from 1922, must be recognized as the start of the "Golden Age of Research" in pelvimetry. The presentation by our Secretary, Dr. Mengert, "Estimation of Pelvic Capacity," before the Section on Obstetrics and Gynecology of the American Medical Association on June 24, 1948, was received with enthusiasm by the group present. He discussed the five components of cephalopelvic disproportion and stressed the importance of the driving force of the uterus. His very practical and valuable contribution to x-ray pelvimetry, adopted by both obstetricians and radiologists on our services in the Navy, was the introduction and definition of pelvic indices demonstrated by lateral and anteroposterior rotentgenograms. He defined the index to pelvic capacity, computed by multiplying the transverse and anteroposterior diameters and expressing the capacity of the various planes in terms of the product of these two diameters.

Dr. Eastman maintains that x-ray pelvimetry for cephalopelvic disproportion alone fails to define the problem in the abnormal or borderline pelvis, since other factors involving distocia occur more often than the essayist has taken into account.

I have asked Drs. R. J. Vaughn, M. H. Macklin, and G. E. Jones of the X-ray Department on the Staff of the Naval Hospital at Newport, Rhode Island, to express their views on this subject. Some of their controversial opinions are clarified by the author—others may be discussed in the concluding remarks if time permits. They express the view that a roentgenogram of the maternal pelvis and the fetus is of questionable value to the roentgenologist when taken in one plane. It is agreed that, in most cases, the true biparietal diameter can be obtained in the normal case, in the lateral projection, that is, in the relatively true gynecoid pelvis, with a fetus of normal size. However, in the case of actual disproportion, the fetal head does not, as a rule, rest in a plane whereby lateral projection will permit measurement of the true biparietal diameter.

Dr. Vaughn, of our staff, who for some years has made a study of the subject, employs the following technique in pelvimetry and cephalometry: (1) flat anteroposterior view with the patient recumbent; (2) anteroposterior view with the patient angled at approximately 45 degrees, as employed by Thoms; (3) lateral projection in the standing posture. From this method, at standard distance, the following information is obtained: (1) biparietal diameter of the head; (2) average net circumference of the fetal head; (3) occipitofrontal diameter. From these radiographs, an average is obtained. It is possible in some instances that the biparietal or the occipitofrontal diameters may not be obtainable. In this case the average net circumference of the skull is calculated. The skull is then assumed to be a sphere, whereupon the passage-passenger ratio is computed.

The comments of our roentgenologists are included to present the method of pelvimetry and cephalometry used on the Service to which I am presently assigned, and to express the observation that techniques and interpretations are variable to a great degree. Techniques, interpretations, and results, are, in my experience, readily amenable to change by the interest and cooperation on the part of the obstetrician with the roentgenologist. Our X-ray Department will be very much interested in Dr. Jacobs' paper.

The essential factor of correlating the clinical with the roentgenological procedures and observations, which Dr. Jacobs has commendably considered, should discourage the practice of routine or promiscuous exposure of mother and fetus to x-ray pelvimetry, thus obviating the possible hazard of any unnecessary irradiation as previously discussed before this body by Dr. Montgomery, and more recently investigated and reported in a publication by Dr. Reeves of the Department of Radiology at Duke University School of Medicine.

Dr. Jacobs is to be commended for his enthusiastic investigation, and for a simple, inexpensive, and relatively accurate technique in pelvimetric roentgenography as related specifically to the title of his paper. His technique and observations on the advantages of the lateral pelvic roentgenogram in the standing posture regarding the method of engagement and stability of the fetal skull are practical and noteworthy. This presentation should assist the trained and experienced, as well as the unskilled, obstetrician in his study of relative fetal maturity and the type of maternal pelvis in the solution of some of the problems of distocia. It should encourage the use of x-ray pelvimetry to correlate our clinical observations and the management of this obstetrical difficulty to the benefit of both patient and obstetrician.

DR. JACOBS (Closing).—In my presentation I did not intend to stress x-ray pelvimetry, although such pictures are necessary for both pelvimetric purposes as well as measurements of the fetal skull. I might say that other means have been used for determining fetal maturity.

Many years ago Scammon and Calkins studied a series of occipitofrontal diameters for such purpose. Since this diameter is seldom depicted squarely on the film, the determinations would be more difficult and less accurate. Roentgenologists in general frequently measure the length of long bones or note the appearance of certain epiphyses in determining the duration of pregnancy or degree of fetal development. Recently an article by Christie and his co-workers appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, in which the authors attempt to determine fetal maturity by the appearance of the ossification centers of the distal epiphysis of the femur and the proximal epiphysis of the tibia. This procedure may have a limited practical value. From my over-all observation, I have found that the easiest and most common characteristic to observe is the biparietal diameter, as has been shown in my lantern slides. For many years, even before I began this investigation, I felt that this information in conjunction with other clinical features previously enumerated was a fairly reliable means of determining fetal maturity and I have resorted to it frequently in doubtful cases.

One should always pay particular attention to the estimated date of confinement, even though occasionally it might be incorrect. Incidentally, as Dr. Willson stresses, most of his cases terminated spontaneously, within about a week of the estimated date of confinement. It is interesting to note that, in my series, the pregnancies terminated spontaneously, practically all of them within 10 days before or after the estimated date of confinement.

Department of Case Reports New Instruments, Etc.

MUCOID CARCINOMA OF THE URACHUS

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THE paucity of reports of mucoid carcinoma arising in the urachus is rather striking, since neither tumors of the bladder nor urachal rests are particularly rare. Begg[1] stated that careful histologic search would reveal urachal rests or cysts in the majority of the cases examined. This fact appears to be substantiated by Saphir and Kurland,[2] who demonstrated the presence of typical tubular structures in the vault of the bladder in the region of the ligamentum umbilicale mediale in 9 of 10 bladders.

These carcinomas arise from the epithelium of the urachal canal, and are, in reality, not tumors of the bladder at all, but merely masquerade as such after they have invaded the bladder mucous membrane. Begg,[3] in 1931, collected 44 cases of assorted urachal tumors from the literature, with only 19 reported cases of mucoid carcinoma. He stated that the colloid carcinoma represents primarily a metaplasia of the transitional epithelium followed by a colloid or mucoid degeneration. The sections appear very much like rectal carcinoma.

Kalo,[4] (1931), Payne and Jones,[5] (1931), Terrier, Craig and Foord,[6] (1936), Begg,[7] (1936), De Waard,[8] (1939), Mattel,[9] (1940), and others have added cases of adenocarcinoma of the urachus to Begg's original list. Hughes and La Towsky[10] (1942) reported 2 cases of mucoid carcinoma of the urachus. Most of those reported had involvement of the bladder mucous membrane.

The embryology of the urachus is thoroughly described by Cullen.[11] The allantois is one of the first structures differentiated in the embryo and is recognized as a recess of the yolk sac extending into the body stalk. In an embryo 2.5 cm. long, a portion of the yolk sac has been definitely differentiated into the digestive tract. Its caudal portion has been carried downward and forward, terminating in the cloaca. The allantois now starts from the cloaca and, after curving upward, passes outward in the body stalk to end in a bulbous extremity near the placenta. By the time the embryo is 7 cm. long, the allantois has been partially separated from the bowel by the urorectal septum. The lower portion of the allantois has been converted into the bladder, and its upper part now passes off the fundus, extending upward and forward, passing out in the cord.

From the foregoing it can be seen that the allantois develops from the yolk sac, that it is one of the earliest structures to make its appearance, and that, after a time, it is carried downward and forward to the cloaca. The bladder develops from the lower portion of the allantois. The upper portion of the allantois is continued upward to the umbilicus and then into the cord. The intra-abdominal portion is called the urachus.

The urachus and allantois soon become solid cords in part of their course, but show an inherent tendency to develop spindlelike dilations at regular intervals. These dilations are characteristic of the urachus and allantois, and may be found at any period in the development of the embryo. These dilations may persist in many persons, and account for small cysts not infrequently noted at operation. The urachus may occasionally remain

patent at birth, and this is attested by the number of children born with a urinary umbilical fistula.

Age Incidence.—In Begg's[3] series, no tumor occurred in a patient younger than 29, and the majority appeared after 50 years of age. In the same series, 80 per cent of the tumors occurred in men.

This case is being reported because the mucoid carcinoma was grossly limited to the urachus and the bladder mucous membrane was not involved.

P. A., a 42-year-old married para 0, gravida i, entered the hospital on June 2, 1952, complaining of severe intermittent lower abdominal pain for 8 days, menorrhagia for 6 months, and frequency of urination. The patient had been told 4 years previously that she had a fibroid uterus which should be removed. Recently, the patient noticed a mass in the lower abdomen that she had not felt previously.

Past history revealed that the patient had had malarial fever in 1938. She had a spontaneous abortion at 4 months' gestation in 1927. Her last menstrual period was on May 28, 1952.

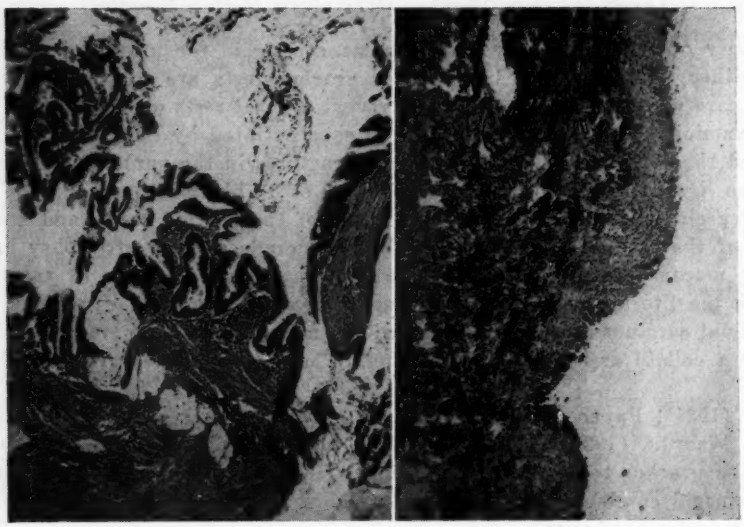

Fig. 1. Fig. 2.

Fig. 1.—Mucoid carcinoma of the urachus.
Fig. 2.—Normal bladder tissue.

General physical examination was negative except for blood pressure of 160/90. The abdomen was distended by a mass in the right lower quadrant near the midline, rising up to 4 cm. below the umbilicus. There was mild tenderness in the left lower quadrant. Pelvic examination showed the uterus to be enlarged to the size of a 3 months' gestation. The mass, felt abdominally, seemed to be anterior and to the right of the uterus. It was thought to be a subserous nodule. There were no adnexal masses or tenderness. Rectal examination was negative except for external hemorrhoids. A provisional diagnosis of fibromyomas of the uterus was made.

A laparotomy was done on June 6, 1952. Operative findings were: an encapsulated tumor 10 cm. in diameter, attached to the anterior abdominal wall by a flat, fibrous stalk about 4 cm. wide. At its upper end, the mass tapered off into the urachus about 2 cm. below the umbilicus. The lower end of this tumor was broadly attached to the dome of the bladder. The tumor was filled with degenerated, gelatinous material. The uterus was enlarged to 12 by 10 cm. and was nodular. The right ovary measured 6 cm. in diameter. On sectioning, it was seen that most of the ovary formed a fibroma, the rest was cystic. The left ovary was cystic. Both tubes were grossly normal. The tumor mass, including the fundus of the bladder,

was removed. The bladder was closed in two layers. A total hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were done.

The patient's postoperative course was uneventful; an indwelling catheter was maintained for 9 days.

Pathologic Report.—Multiple fibromyomas of the uterus; proliferative endometrium; fibroma of right ovary; normal tubes and cervix; encapsulated mucinous-cell adenocarcinoma attached to the wall of the bladder, probably arising in a urachal rest.

In order to rule out malignancy of the gastrointestinal tract, a gastrointestinal series and a proctoscopic examination were done on the eleventh postoperative day. Both were negative. The patient was discharged on the twelfth postoperative day. The wound was healed. Abdominal and pelvic examinations did not show any masses, induration, or tenderness.

Microscopic Report.—The entire specimen was very friable and contained brownish, mucoid material. Histology: The wall consisted in part of fibrous tissue with a laminated appearance. In many places, necrosis had taken place and the tissue presented a homogeneous appearance and took the stain poorly. Portions showed glandlike spaces lined with one or more layers of low columnar epithelium exhibiting mucinous secretion. The nuclei of the epithelial cells were oval and vesicular, and deeply stained. In some areas, the epithelium had proliferated to some degree (Fig. 1).

Comment.—There is no doubt that we were dealing with a multilocular cyst of the urachus that had become malignant. This growth was not intraperitoneal, and was not connected with anything in the peritoneal cavity. Its pedicle sprang from the top of the bladder. During the removal of the tumor, a large part of the peritoneum and transversalis fascia of the anterior abdominal wall had to be sacrificed. The portion of the fundus of the bladder adjacent to the tumor was removed to make sure that we were not dealing with a carcinoma of the bladder (Fig. 2). The mucous membrane of the bladder was not involved. This tumor evidently originated in the urachus. The treatment is surgical, and the operative specimen should include the umbilicus, a wedge-shaped block of transversalis fascia, the peritoneum, and at least the fundus of the bladder.

I wish to thank Dr. Solomon Weintraub for his pathological study of this case.

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CONGENITAL ANOMALY OF THE UTERUS

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THE present communication is the report of an unusual congenital developmental anomaly of the uterus due to lack of fusion of the Müllerian ducts and the absence of the lowermost portions. There were two uterine bodies, each with a normal tube and ovary and secretory endometrium, and absence of cervix and vagina. In the article by Jarcho,[1] this anomaly is not mentioned. A review of the literature subsequent to his publication failed to reveal the report of a similar case.

The patient was a nulliparous Negro woman, 25 years old. At 14 years of age, there were periods interpreted as vaginal bleeding, occurring at monthly intervals and lasting three days. These episodes occurred for seven months, then ceased and never recurred.

The next year, a gynecological examination revealed an imperforate hymen. Internal generative organs could not be palpated on rectal examination. A hymenotomy was performed and a short vaginal canal 2 cm. in depth was found. No structure identifiable as cervix could be seen and internal organs could not be identified. A laparotomy was done and the findings diagnosed as uterus didelphys with normal tubes and ovaries.

Four years later, at 19 years of age, marriage was contemplated and medical advice sought. A McIndoe operation for construction of an artificial vagina was carried out in February, 1946, using a full-thickness skin graft. The result was excellent, a canal approximately 10 cm. deep being obtained.

Six years later, on April 3, 1952, she was admitted to City Hospital. For the last six years, she had episodes of intermittent lower left quadrant pain, at irregular intervals and lasting for a variable length of time.

She was a well-nourished, well-developed Negro woman of normal feminine habitus. The positive findings were limited to the genital tract. The vagina was pigmented, moist, about 10 cm. deep and easily admitted two fingers. A uterus could not be palpated. In the right adnexal region, a mass, apparently normal ovary, was felt. On the left side, a mass about 3 inches in diameter was found, hard, irregular, slightly tender and freely movable. An excretory urogram failed to reveal any abnormality. The clinical diagnosis of tumor of the left ovary, possibly dysgerminoma, was made and laparotomy advised.

Operative Findings.—On each side of the midline a corpus uteri was present, each with an attached normal tube and ovary, round and uterosacral ligaments. They were separated from each other by a space 2 inches wide, were completely unattached to each other and were not attached to the vagina. Nothing resembling cervix could be found. The body on the right measured 1 by 1 by 2 cm. The left body was 9 by 9 by 7 cm. and was deformed by multiple fibroids. The left ovary had a corpus hemorrhagicum; the right ovary was normal. There were neither adhesions nor evidence of endometriosis. Both uteri were removed, the ovaries allowed to remain in situ.

Pathological examination revealed a cavity in each body starting at the horn, measuring 2 cm. in length and ending blindly. The endometrial glands were lined by tall homogeneous moderately clear cells with central nuclei. The stroma was cellular. There was neither fresh nor old blood. Cervical tissue was absent.

Diagnosis.—Double uterus, fibromyomas of left uterus, secretory endometrium, aplasia of cervix.

Comment.—The presence of two separate uterine bodies, each with a single horn and attached tube and ovary, and the absence of cervix and vagina, indicates complete failure of fusion of the Müllerian ducts and absence of the lowermost portions.

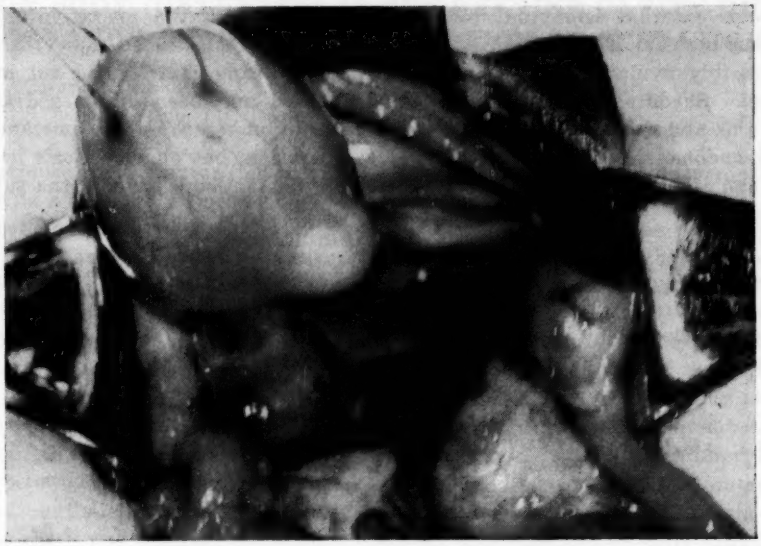

Fig. 1.—View of the operative field. The left uterus, retracted by a tension suture, is enlarged by fibroid masses. Behind it can be seen the ovary with a corpus hemorrahgicum. The right uterus is smaller, the ovary normal.

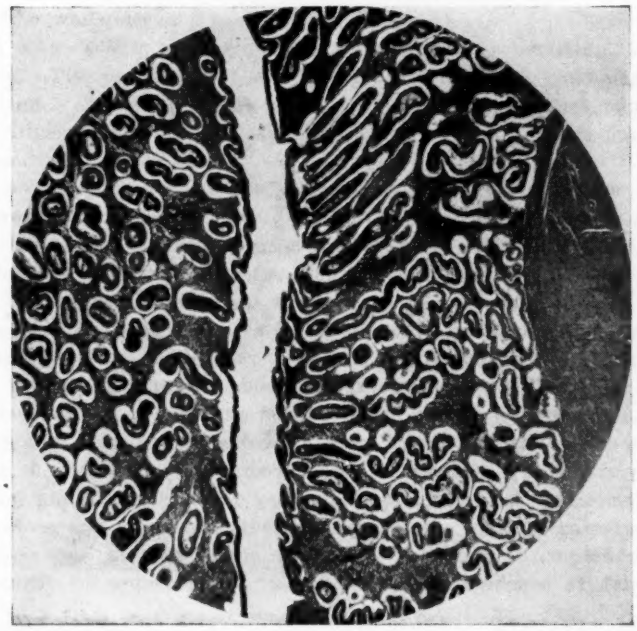

Fig. 2.—Microscopic section of the endometrium showing an early secretory phase.

The episodes of bleeding which occurred at the age of 14 are difficult to explain. They could not have been true menstrual uterine bleeding, since it was later shown that there was no communication between the uterine cavities and the rudimentary vagina and there was fur-

thermore an imperforate hymen. Bleeding from hemorrhoids is a possible explanation. The periodicity of the bleeding and the failure of any observer to find hemorrhoids later mitigates against this interpretation. There remains the possibility of vicarious menstruation, an admittedly unsatisfactory explanation.

Although external menstrual bleeding never occurred, the operative finding of a corpus hemorrhagicum and the presence of a secretory endometrium imply that menstruation and possibly ovulation had been present. The uterine cavities did not have old retained blood. Shedding, however, may have occurred and been discharged through the tubes into the abdominal cavity. One would expect, under these circumstances, to find evidence of endometriosis. None was found at operation, but endometriosis in the Negro is unusual and its absence does not disprove retrograde spillage through the tubes.

Summary and Conclusions

A unique case of double uterus with normal tubes and ovaries and absence of cervix and vagina is reported. The patient, a Negro woman, had probably menstruated and possibly ovulated, followed by retrograde spillage into the abdominal cavity not resulting in endometriosis.

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FOREIGN BODY (CATHETER) IN THE UTERINE CAVITY DURING PREGNANCY WITHOUT INTERRUPTION OF GESTATION*

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(From the Peoples Hospital, Akron, Ohio)

THE occurrence of a foreign body in the pregnant uterus without interruption of the gestation is a relatively uncommon incident.

That foreign bodies inserted into the uterus may pass, or may be passed, through it is known. Bateman[1] has reported a case of a woman inserting a catheter into the pregnant uterus and, apparently, through it. The catheter was removed from the abdominal cavity, and the gestation continued to term.

The present case is that of a 28-year-old woman who was seen for the first time on Jan. 12, 1951, with a chief complaint of abdominal pain.

Present Illness.—The last menstrual period was in July of 1950. Because she was unmarried, the patient attempted to abort during early pregnancy by taking quinine and castor oil. She admitted that four or five weeks prior to admission she attempted to insert a catheter, but did not believe she was successful, as she caused no bleeding or gushing of water. Despite this, she had continued to work and feel fairly well until Jan. 1, 1951. At that time she quit work as she "was tired all the time." Nausea and vomiting of early pregnancy were subsiding.

Three days prior to admission she began to have abdominal pain, most severe in the lower right side, and pain across the lower back. Pain had persisted, and at the time of admission was all over the abdomen, especially in the hypogastrium. A "bearing down" pain over the bladder was noticed.

The present episode was not associated with nausea or vomiting, but her appetite had not been good. The patient had been having regular bowel movements, but none on the day of admission. There was some urinary frequency during pregnancy, accentuated since the present illness, and this was associated with burning. There had been no chills, but the patient said she felt warm.

There were no previous pregnancies, and the rest of the past history was irrelevant.

Physical Examination.—Temperature was 100.4° F., pulse 92, respiration 20, blood pressure 116/70. She was an obese white woman who appeared to be in moderately severe pain. The remarkable findings were limited to the abdomen and pelvis.

Abdomen: The entire abdomen was tender to palpation with rebound tenderness. The uterus was enlarged to the size of a five to six months' gestation. It was somewhat difficult to outline because of its tenderness. No fetal heart sounds were heard, nor were any fetal movements noted. The upper abdomen was moderately distended. The intestines were gas filled according to percussion; normal bowel sounds were present.

Pelvis: Speculum examination revealed a large amount of white discharge exuding from the external os of the cervix. There was no sign of trauma. The cervix was only slightly tender to palpation and movement. It was uneffaced and closed. Minimal tenderness was elicited in the fornices, and no masses other than the uterus could be palpated.

The impression was that of pelvic peritonitis following attempted abortion, and an intrauterine pregnancy of approximately six months. No evidence of fetal life had been shown.

Laboratory Examination.—The urine was negative except for 15 white blood cells per high-power field. Analysis of the blood showed red blood count 4 million; hemoglobin 78 per cent, or 12 Gm.; white blood count 23,300, with stab forms 14, segmented cells 77, lymphocytes 7, monocytes 2. The Kahn reaction was reported as negative.

*Presented at a meeting of the Akron Obstetrical and Gynecological Society, July 18, 1952.

Therapy and Course.—The patient was placed on a liquid diet, with aqueous procaine penicillin, 300,000 units intramuscularly twice a day, and aureomycin, 250 mg. four times a day, and was given 1,000 c.c. of 5 per cent glucose in normal saline on admission.

She was afebrile after the day of admission. The day after admission her only complaint was moderate tenderness all over the abdomen. She was retaining fluids. No fetal heart tones were heard. An enema considerably decreased the distention. A flat plate of the abdomen showed an indistinctly outlined fetus of about six months' gestation. There was a foreign body resembling a rubber catheter situated in the region of the fundus. It measured about 21 cm. in length and curved to the left. The tip was situated at the level of the lower segment of the sacrum (Fig. 1).

Fig. 1.

On the next day the patient stated that a catheter had been inserted three weeks prior to admission. Her condition was improved. It was planned to carry the patient unil she was recovered from the present episode, and then evaluate the possibilities of evacuating the uterus. It was feared that the catheter might erode through the uterus, if it were permitted to remain in situ.

X-rays on the following dates were reported thus: Jan. 15, 1951: "Examination of the abdomen in the lateral projection again reveals the previously described opaque foreign body which appears to lie within the cavity of the uterus, although we cannot state with complete assurance that no perforation has taken place." Jan. 16, 1951: "Re-examination of the abdomen in the upright position shows no evidence of free air within the peritoneal cavity. The findings remain essentially as previously."

The patient continued to improve and on January 19 (seven days after admission) an unsuccessful attempt to induce labor was made, using calcium gluconate, 10 grains intravenously, castor oil, quinine, and an enema.

The patient felt well from then on, and it was decided to attempt no further interference and to follow her closely in the outpatient clinic. She was discharged from the hospital on Jan. 22, 1951.

She was seen regularly at the outpatient clinic. At her first visit the only additional history obtained was that of a spontaneous abortion in 1948. Fetal movement was first noted on Jan. 30, 1951. The prenatal course continued uneventfully. On March 29, the patient stated that she had passed the catheter four or five weeks ago.

Labor began on April 6, 1951. On admission an x-ray showed a normal fetus, and there was no evidence of the catheter. The patient had a normal labor and uneventful delivery of a living, apparently normal male infant, who weighed 6¾ pounds. Manual exploration of the uterus revealed no defects. The postpartum course was uneventful. An examination on May 31, 1951, revealed a normal pelvis.

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SURVIVAL OF PREGNANCY FOLLOWING BILATERAL OOPHORECTOMY AT TWO MONTHS

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(From the Good Samaritan Hospital)

TOTAL removal of ovarian tissue during pregnancy with survival of the pregnancy has been frequently described in the literature. It is of sufficient interest to justify the report of the individual case.

Corner and Hartman have shown through animal experimentation that in the monkey the corpus luteum of pregnancy may be removed as early as the twenty-fifth day of gestation without interrupting the pregnancy. It is the generally accepted view that ablation of the ovaries before the end of the first trimester may lead to abortion since elaboration of corpus luteum substance by the placenta does not occur before this period of gestation.

There are instances in which case reports would seem to contradict this notion. However, since the majority of tumors accompanying pregnancy are dermoids or simple cystomas and not malignant, postponement of operation until the end of the third month of pregnancy is advisable. Large ovarian tumors, development of pain, or instances of torsion may modify this rule.

Within the past year we have encountered a case in which bilateral oophorectomy was performed at the end of the second month of pregnancy, the pregnancy subsequently progressing to term with the delivery of a living baby.

This patient, a primigravida, 30 years of age, was seen in consultation on May 23, 1951, because of persistent lower abdominal pain with vaginal spotting and mass in lower abdomen. The patient stated that for a period of ten years she had been conscious of a mass in the abdomen and that when recumbent she could feel the "tumor move from side to side" as she shifted position. For a period of one year the menses had occurred every 10 to 18 days and had lasted 3 to 4 days. The patient's last menstrual period (normal) occurred on March 14. She was married on March 24.

She was admitted to Good Samaritan Hospital, on May 23, 1951. As previously mentioned, she complained of a mass in the lower abdomen, pain, and slight vaginal bleeding. She was afebrile and laboratory studies were essentially normal.

Abdominal examination revealed two distinct masses, one felt above the pubic bone and to right of the midline; a second mass which was remarkably mobile could be both seen and felt in the left lower quadrant. Vaginal examination showed the cervix to be somewhat softened and closed, and the mass described as to the right of the midline was softened, symmetrical, and suggested a pregnant uterus. There was a third mass deep in the cul-de-sac and extremely tender.

On May 25, 1951, the abdomen was explored. The uterus was enlarged to the size of a 2 to 3 months' pregnancy. There was considerable free fluid within the abdominal cavity. Both ovaries were involved in semisolid tumors. The right ovary was the smaller—it had undergone partial torsion, was adherent in the cul-de-sac, and the serosal covering showed considerable inflammatory reaction. The left ovary was freely movable on the left side of abdominal cavity.

Both ovaries were removed. The report of the pathologist was as follows:

Gross Description.—The specimen consisted of two cystic ovaries. One was globular in shape and measured 4.5 cm. in diameter. The other was ovoid and measured 8 by 5 by 6 cm. Each on section was found to be filled with cheesy or buttery material and in one of them there were remnants of what was obviously calcified tissue. No tooth was seen.

Microscopic Examination.—The sections of the two dermoid cyst walls showed a lining surface of stratified squamous epithelium richly keratinized. Numerous hair shafts were intermingled with the keratohyaline material. The supporting ovarian stroma was atrophic and compressed. There was no evidence of malignant tumor. A considerable amount of lobulated adipose tissue was present below.

Diagnosis.—Dermoid cysts of ovary, bilateral.

Recovery was uneventful. The patient was given daily doses of 20 mg. of progesterone. She was discharged on the ninth postoperative day. She was given 20 mg. of progesterone twice a week for one month following her discharge from the hospital. She noted quickening the early part of August, 1951.

On November 19, the membranes ruptured and, after a rather protracted labor of some 36 hours, a living baby was delivered by outlet forceps.

The patient has never menstruated since completion of her pregnancy, and it may therefore be assumed that all ovarian tissue was removed at the time of operation.

LIPOMA OF THE UTERUS

JOHN W. ROBERTSON, M.D., AND HARRIS GERBER, M.D., PHILADELPHIA, PA.

(From the Department of Pathology, Albert Einstein Medical Center, Northern Division)

LIPOMAS of the uterus are extremely rare, and therefore worthy of record. They occur either in a pure form, consisting of adipose tissue with a minimum of supporting stroma, or as mixed tumors, containing, in addition, muscle, fibrous tissue, or cartilage. Those of the "pure form" are slightly less common.

The first case reported is apparently that of Lebert[1] in 1857. Since then, a number of collective reviews have been published. The most recent is that of Ikonomou[2] in 1947. He reported a single case and collected from the literature 22 cases of "pure" lipoma, and 30 of the "mixed" type. Since then Howe and Kellert[3] have reported a case of the "mixed" type, and Decker[4] and Bruntsch[5] have each reported a case of "pure" lipoma, the latter associated with a carcinoma of the corpus.

The incidence of this tumor is impossible to ascertain, except that it is exceedingly rare. The case we are reporting is the only example found in the records of this hospital, where over 3,500 hysterectomies have been performed in the past 20 years.

Case Report.—M. M., a 65-year-old white woman, gravida vi, para v, was admitted to the Jewish Hospital with a chief complaint of pressure in the lower abdomen and an uncomfortable feeling in the rectum. Her menses had been normal until menopause at 59 years. Her last pregnancy had been when she was 26 years of age. The remainder of her history was irrelevant. Physical examination revealed a cystocele with a second-degree prolapse, and slight enlargement of the uterus.

A vaginal hysterectomy, and an anterior and posterior colporrhaphy were performed. Recovery was uneventful, and she was discharged on the fifteenth postoperative day.

The surgical specimen consisted of the uterus, with cervix. It was symmetrically enlarged to the left, measuring 8 cm. in length and 7.5 cm. across the fundus. The surface was smooth. The bulk of the enlargement was due to a circumscribed soft yellow tumor, 4 cm. in diameter, located along the left lateral aspect of the myometrium. It was surrounded by myometrium, with a sharply outlined border. The cut surface of the tumor was homogeneously bright yellow, vaguely lobulated, and bulged above the surrounding tissue. Also present in the myometrium were several small, firm, grayish white, whorled nodules, ranging from 0.4 to 0.8 cm. in diameter. The uterine cavity was only slightly distorted. The endometrium was focally hemorrhagic. It presented three thick, soft, sessile polyps, and one pedunculated polyp. The largest measured 2 by 1 by 0.3 cm. The cervix measured 2 cm. in diameter; it was focally hemorrhagic, and contained small, thin-walled cysts.

Sections from many areas of the tumor revealed mature fat cells, with eccentric nuclei. There was minimal supportive fibrous connective tissue. The border against the myometrium was sharply outlined and the myometrium was compressed.

The small nodules were characteristic myomas. The endometrial polyps were cystic; the cervix contained mucinous cysts.

The pathological diagnoses were: Lipoma of uterus; myomas of the uterus; benign, cystic endometrial polyps; cystic cervix.

Comment.—Most of the lipomas of the uterus have been found in older women, usually after the menopause. They are probably of little clinical importance, most having been incidental discoveries. Only one of the reported cases has been considered malignant.

The histogenesis of this rare tumor remains in some doubt. Normally, the uterus contains no adipose tissue. Brunnings,[5] who reported a case in 1899, suggested metaplasia of smooth muscle into fat cells. Seydel[6] held that lipomas could arise only from displaced lipoblastic tissue. This explanation has been accepted by most subsequent authors. Elkins and Haythorn[7] regarded the fibrous and muscle tissue in the "mixed type" as accidental inclusions in the tumor, and hold that all these tumors should be included in the diagnosis "lipoblastoma uteri."

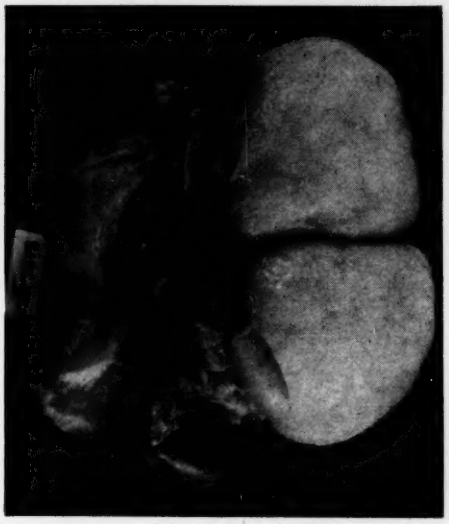

Fig. 1.—Opened uterus, showing bisected intramural lipoma.

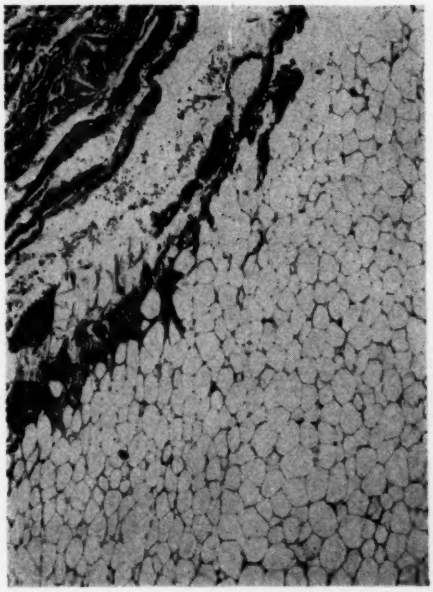

Fig. 2.—Section of lipoma, showing the normal adipose tissue, and the sharp border against the myometrium. (Hematoxylin and eosin. ×50.)

Summary.—A case of pure lipoma of the uterus (according to the classification of Ikonomou) is reported. This makes the twenty-fourth such case. These tumors give no specific symptoms, and rarely are of clinical significance. The prevailing theory is that they originate from congenitally displaced adipose tissue.

We are indebted to Dr. P. Sales, whose private case this was, for the clinical history.

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Department of Reviews and Abstracts

CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

Review of New Books

EDITED BY PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

Gynecology

Manual of Gynecology. By E. Stewart Taylor, M.D., Professor and Head of Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver. 204 pages with 70 illustrations. Philadelphia, 1952, Lea & Febiger. $4.50.

Manual of Gynecology presents in a very compact manner the fundamentals which should be combined with bedside and clinic teaching. All of the chapter headings in more voluminous texts are included and in addition one in the use of hormone preparations in gynecology and orientation as to proprietary hormone products.

Written primarily as a guide for students and general physicians, this text is necessarily a bit dogmatic. With the author's sound judgment, this is an asset to the teaching manual. The bibliography at the end of each chapter is recent and well chosen, serving as a stimulus for the more curious.

Modern concepts have been utilized in diagnosis as well as treatment. It is refreshing to read such unequivocal statements as "the retroverted uterus does not cause backache in the female." The preferred medical management or operation is noted without technical details.

There may be some disagreement as to the advisability of even requesting a patient who gives a history of habitual abortion to desist from intercourse throughout pregnancy. The Albert Smith pessary is labeled Smith-Hodge, if the reviewer is seeking just one error.

As a prospective text for medical students or a handy reference for the general physician, this practical and concise book embodies the basic essentials of the subject.

EUGENE H. COUNTISS

Gynecologic and Obstetric Pathology With Clinical and Endocrine Relations. By Emil Novak, M.D., Assistant Professor Emeritus of Gynecology, Johns Hopkins Medical School. Third edition, 595 pages with 640 illustrations, Philadelphia, 1952, W. B. Saunders Company.

Under the new title of *Gynecologic and Obstetric Pathology*, thirteen out of thirty-four original chapters of this book remain essentially unchanged. In the remaining chapters there have been extensive additions in the form of several colored plates and numerous black and white plates. The text has been revised, taking into consideration the recent literature, and each chapter contains an up-to-date bibliography. The subject of carcinoma in situ of the cervix and its relationship to cervical cytology smears is thoroughly discussed. There is added discussion of the probable relationship of hyperplasia of the endometrium to cancer in that tissue. Also new is the consideration of pregnancy changes in the various organs of reproduction. Dr. Novak also comments on recent work on alka-

line phosphate in the endometrium. In the chapter on granulosa-cell tumors, there are several additions, including recent experimental data. The chapter on hydatidiform mole and choreonepithelioma contains a sound discussion of the clinical aspect of these problems.

Finally, there has been an excellent chapter added on the common breast lesions which are of interest to the gynecologist.

These additions have necessitated adding twenty-five new pages to the book with a slight increase in format.

In my opinion, the third edition of Dr. Novak's book remains the best compilation of gynecological and obstetrical pathology. It is concise and clear enough to be of great benefit to the medical student and, at the same time, it contains the detailed information necessary for use as a standard reference book by the experienced pathologist.

J. P. A. LATOUR.

Physiological Bases of Gynecology and Obstetrics. By S. R. M. Reynolds, Ph.D., Sc.D., Staff Member, Physiologist, Department of Embryology, Carnegie Institute of Washington. 153 pages. Springfield, Ill., 1952, Charles C Thomas. $5.50.

The *Physiological Bases of Gynecology and Obstetrics* by S. R. M. Reynolds is, in essence, a review of what is known of uterine function. It is written by a physiologist who has the fortunate ability to condense and to present a complex subject in a manner which is understandable and appealing not only to the student of uterine physiology but also to the obstetrician-gynecologist who wishes to learn more about the basic physiology of the female genitals. It is comprised of fifteen lectures which the author presented to postgraduate physicians at the Facultad de Medicina de Montevideo.

The introductory lecture points out the necessity for integrating the study of uterine growth, uterine motility, and uterine vascularity. The pertinent observations are made that not only are these basic physiological mechanisms interrelated and interdependent but that all uterine functions are inextricably related to each other. In this respect the Montevidian expression "gynecotokology," which etymologically combines gynecology and obstetrics, might advantageously become more familiar to clinicians and investigators whose interests tend to limit their views to one aspect of genital morphology or function.

Approximately half of the book is a review of the physiological bases for uterine contractility and dilatation of the cervix, uterine action in abnormal labor, uterine growth and circulation during pregnancy, the effects of uterine distention, fetal maturity at birth, and the onset of labor. Two lectures are devoted to the ovarian vasculature. The physiological bases for menstruation and the somatic vascular actions of steroid hormones are discussed. In the lecture on the endocrine effects of hysterectomy the essayist leaves the field of mammalian physiology to discuss a subject which is primarily endocrinological.

As the author states, the lectures are intended for the busy gynecotokologist who lacks the time to make a detailed study of the extensive literature or to read detailed monographs. There are few references and there is no comprehensive bibliography. Some of the essays are essentially synopses of portions of the author's well known monograph, *Physiology of the Uterus.* The latter is a compendious exposition and correlation of current concepts of uterine physiology and uterine hormonal responses. In it the interested reader will find a comprehensive bibliography and a detailed discussion of most of the subjects covered in the lectures.

JOHN W. HUFFMAN

Toxemias of Pregnancy. By William J. Dieckmann, S.B., M.D., Chief of Service of the Chicago Lying-in Hospital. Second edition, 710 pages with 85 illustrations and 1 color plate, St. Louis, 1952, The C. V. Mosby Company. $14.50.

Dieckmann's second edition of *Toxemias of Pregnancy* is a most valuable contribution to obstetric literature. The author has accumulated the important research of a large number of investigators. These results are analyzed in the light of his own considerable

experience. The result is a critical and clear study that should be of great value to all physicians treating this obstetric problem.

The author advises correcting the diagnosis and classification after adequate postpartum observations. The chapter on geographic distribution, including a discussion of incidence in relation to diet, temperature, and humidity is of particular interest. The chapters on pathology and physicochemical determinations, including weight variations, blood pressure, and renal physiology, are an indication of the exhaustive study made. Significant is the conclusion that renal function tests are of little help in differential diagnosis. The endocrine glands and their relation to the toxemias are discussed. The author believes that there has not been sufficient follow-up study on reported hormonal studies to confirm the type of toxemia discussed.

The discussion of edema in pre-eclampsia and eclampsia was of most interest to this reviewer. Following a review of many studies the author states: "The conclusion to be drawn from these studies is that if the pregnant patient were to restrict the sodium and potassium intake throughout pregnancy and drink sufficient fluids to ensure a urinary volume as mentioned above, pre-eclampsia would be less likely to occur and might even be prevented." The use of common terms is of great importance. Sometimes the word fluid is used when water is meant. Some fluids contain sufficient base or sodium to defeat the purpose for which they are given; such fluids cannot be given freely in treating the toxemias. Conversely, when such fluid, water plus electrolyte, is not excreted, edema results. The author frequently uses the term water as a synonym for salt plus water.

The importance of cell function is stressed and the possible relationship to disturbance of cell function in producing convulsions, increase in blood pressure, coma, and hyperpyrexia is discussed. The author suggests that sodium retention, that is, increased concentration, may disturb cell function. He points out that inadequate amounts of available water will not permit the kidneys to excrete necessary amounts of sodium.

There is a contradiction in the section dealing with diet. The text states that the diet outlined for pre-eclampsia is of acid-ash composition, low in sodium and potassium. Later the text states that the diet has an excess of base content.

The references are voluminous. The conclusions are noteworthy as they are drawn from a compilation of the most important research in this field, and from personal control studies by the author. The number of new facts developed since 1940 is surprisingly low. The author suggests that more would be known of pre-eclampsia-eclampsia if the research problem could be a concerted study by a number of investigators, several taking the same problems, but pooling results for analysis and study. This is an excellent suggestion and should be given serious consideration. Then the hope that pre-eclampsia would be less likely to occur and might even be prevented might become an accomplished fact.

As stated in the first edition, the book was written with two objectives in mind: to acquaint the obstetrician with some of the recent contributions on physiology pertaining to obstetrics, and to acquaint the investigator, untrained in obstetrics, with some of the physiology and pathology of obstetrics. The reviewer feels that this is a splendid study of the toxemias and that all objectives have been attained.

FRANK L. MCPHAIL

Lehrbuch der Geburtshilfe. By Heinrich Martius, Director of University Woman's Clinic in Goettingen; with the collaboration of Werner Bickenbach, Director of University Woman's Clinic at Tuebingen. Second edition, 770 pages with 786 illustrations. Stuttgart, 1952, Georg Thieme. DM 58.80.

This textbook of obstetrics is intended to serve as a companion to the author's other volumes on the subject of obstetrics and gynecology. Much fundamental material is presented in *Grundlagen der Gynäkologie;* obstetric operations are discussed in still another book. Hence these two subjects are omitted from the present textbook.

In common with other works by Prof. Martius, this volume is clearly written and beautifully illustrated. In the opinion of this reviewer, however, inadequate attention is

paid to the major medical complications of pregnancy. Heart disease, diabetes mellitus, and the anemias of pregnancy receive far too little attention. The section on toxemias of pregnancy is not clear to a person accustomed to the American viewpoint. True toxemia of pregnancy is not adequately differentiated from chronic hypertensive disease. Very few American obstetricians would agree with the author's recommendation of a low-protein diet in the management of toxemia.

The sections on pelvic contraction and other pelvic deformities are excellent. Nevertheless, roentgen pelvimetry is not accorded the position to which this reviewer believes it is entitled.

There is an occasional statement in this book which most American observers would regard as an outright error. For example, the author states that a hemoglobin of 60 per cent Sahli may be regarded as normal in pregnancy.

By and large it may be said that this volume expresses contemporary German thinking. In the main, it is a worthy companion to Prof. Martius' other volumes in the field of obstetrics and gynecology.

BRUCE A. HARRIS, JR.

Pathological Syndromes of Pregnancy and the Puerperium (Syndromes pathologiques de la gravido-puerpéralité). By E. Lévy-Solal, Professor, and J. Grasset, Associate Professor at the Faculté de Médecine de Paris. 573 pages with 219 illustrations, Paris, 1952, Masson et Cie. 4,200 Fr. francs.

The recent trends and the considerable progress realized in these last years in the diverse branches of medicine and basic sciences have had important repercussions in the field of obstetrics and reproductive functions. Many classical theoretical notions had to be revised, many new clinical entities had to be described, many very interesting therapeutic attainments had to be realized. It has become a necessity to furnish the practitioner with a simple and concise explanation of the actual concept and the essential practical data which he can apply to his everyday practice. This is achieved in this book.

The authors deviated from the usual clinical presentation of the subjects, starting from the diverse general syndromes or their particular varieties, to arrive at the nosological diagnosis, and, from there, to establish the general lines of rational therapeutics.

On a strictly clinical basis are successively envisaged the hemorrhagic syndromes, the painful syndromes, the infectious syndromes, the traumatic syndromes at all stages of gestation, labor, and the puerperium, where they can be observed. According to the time of their appearance, the syndromes often show particular trends and pose problems in diagnosis, prognosis, and therapeutics of great interest.

The book is not a manual. The new and interesting data particularly useful for the formulation of a diagnosis or the establishment of therapeutics are voluntarily amplified. To understand better certain new data, considerable space has been given to basic physiopathological notions which constitute the surest basis for sound therapy.

In the book the practitioner will find a sound clinical guide for immediate or future reference. The student also will find it useful. Each chapter is preceded by a brief summary of the principal theories to facilitate comprehension of the mechanism of production of the clinical manifestations observed.

The book is richly illustrated, which helps the reader considerably in understanding the text. The 219 photographs in black and white are for the greater part taken from the Museum of the famous Baudelocque Clinic of Paris. They are of very high quality and many of them are printed on a rich glossy paper that does them justice.

The book is divided into five chapters, each subdivided into many sections. It is printed in excellent type, small, large, light faced or heavy faced, Roman or in Italic, according to the importance attached to the meaning of a sentence. References are thus easily found.

A great improvement is shown by the French publishers who are coming back into their own in the presentation of their books and magazines.

LÉON GÉRIN-LAJOIE

Die Wertheimsche radikal Operation beim Carcinoma Colli Uteri. By Professor Doctor Paul Werner and Doctor J. Sederl. 42 pages with 32 illustrations. Wien, 1952, Urban and Schwarzenberg.

The foreword to *The Wertheim Radical Operation for Carcinoma of the Cervix,* written by Paul Werner, the last pupil of Wertheim, handles briefly the history of the development of the procedure, through the period of relative disuse due to the advent of radiation therapy to its rebirth in the last decade.

The introduction deals with some misconceptions as to the original radical procedure performed by Wertheim. The footnotes on pages one and twelve are particularly enlightening, reiterating the fact that Wertheim did include gland dissection in the original procedure. This section includes also a few words on preoperative preparation and anesthesia in the Vienna clinic.

The first section deals with the operation in detail and for the most part correlates the thirty-two illustrations which occupy the major portion of the book. Preservation of blood supply to the urinary tract and the principles of handling the ureter and bladder are noted. Postoperative care and radiation therapy are covered briefly.

The thirty-two illustrations by E. Lepiers are diagrammatic and quite well done. Certainly little has been omitted in the effort to clarify the extent and technique of the procedure. This portion could well serve as a manual.

The final chapter describes the authors' results in the treatment of 406 patients with carcinoma of the cervix from 1940 to 1950. It is amazing to note that the operability was 76.35 per cent. Also of interest is the comment on the frequency of inflammatory reaction following biopsy, and the subsequent increase in difficulty of the procedure. The use of transfusion is apparently limited almost exclusively to the preoperative period.

Variations in the procedure, such as resection of bowel and bladder and reimplantation of the ureter into the bladder, are carried out in those cases of more advanced disease (Stages III and IV). The primary mortality in the 300 cases operated upon was a low 6 per cent, and each of the 18 fatal cases, with cause of death, is described briefly. Statistics on the number of instances of gland involvement and fistulous complications are given. The excellent five-year salvage of 59.39 per cent is compared with results from other clinics.

The closing paragraphs deal with general issues in the diagnosis and treatment of carcinoma of the cervix.

For anyone interested in the treatment of carcinoma of the cervix, particularly from the operative point of view, the monograph is highly recommended.

J. DONALD WOODRUFF

Obstetrics

Lehrbuch der geburtshilflichen Operationen. Edited by Prof. Dr. E. Anderes, Direktor der Universitats Frauenklinik, Zurich. 416 pages with 175 illustrations. Basel, 1952, S. Karger. Swiss fracs 52.

This is the third book in a series which bears the general title *Textbook of Obstetrics and Gynecology.* The first book in the series was the *Textbook of Gynecology,* which was prepared by Hans Guggisberg; the second was the *Textbook of Obstetrics* written by Th. Koller; and this book is the third one. The author had six collaborators. The introductory section dealing with indications for obstetric operations and the chapters on dangers to the mother and child, as well as the section on special operative procedures during labor, were written by Anderes. The sections on preparations for obstetric operations and repair of injuries during labor were contributed by H. Winzeler. The portion dealing with obstetric operations including sterilization after interruption of pregnancy and normal labor, as well as the chapters on operations in the postpartum period and medicolegal obstetrics were prepared by E. Glatthaar. The sections on special operative procedures, treatment of uterine

rupture, and asphyxia of the newborn were written by H. Sauter. The chapter on birth injuries of the child was contributed by H. Willi and the chapter on the treatment of blood loss was written by M. Laszczower and H. Winzeler.

Even though all the illustrations intentionally show ungloved hands, the authors properly recommend the use of long gloves for intrauterine manipulations. They favor the use of direct infiltration anesthesia for many vaginal deliveries and cesarean section. As one of the methods of terminating pregnancy from the fifth to the seventh month, the use of a metreurynter filled with glycerin and placed extraovularly is described and illustrated, but vaginal hysterotomy or even abdominal hysterotomy is preferable. The authors mention these surgical procedures. The Hicks version is described and illustrated for the treatment of total placenta previa but, in my opinion, cesarean section is far safer for both the mother and the baby. The authors do not describe the extraperitoneal cesarean section because "in most cases it has lost its justification." The authors prefer the low cervical or, as they call it, the isthmical transperitoneal cesarean section. Laminaria tents are described and illustrated for the purpose of dilating the cervix but these tents are not used in the United States. Among the procedures recommended for sterilization one fails to find the Pomeroy method or the Irving procedure. Six illustrations are devoted to the delivery of a breech by means of a metal hook, which can be a dangerous procedure.

In spite of these minor criticisms, the book is an excellent one. It contains a great deal of valuable information. There are 175 beautiful and instructive illustrations, many of which are in color, and even though six men collaborated, the book is smoothly written. It will surely be popular in German-speaking countries.

J. P. GREENHILL

Synopsis of Obstetrics. By Jennings C. Litzenberg, B.Sc., M.D., F.A.C.S., late Professor of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis. Fourth edition, revised by Charles E. McLennan, M.D., Professor of Obstetrics and Gynecology, Stanford University School of Medicine, San Francisco. 378 pages with 157 illustrations. St. Louis, 1952, The C. V. Mosby Company. $5.50.

It is unusual that the essentials of a subject are so completely covered as in this *Synopsis of Obstetrics* by the late Dr. Litzenberg. Since McLennan assisted in the first edition, he is well qualified to revise the fourth one.

By deletions and complete rewriting of certain major sections, particularly those concerned with the early life of the ovum, endocrine physiology, Rh isoimmunization, regional anesthesia, roentgen pelvimetry, and pregnancy toxemia, this work has been modernized with but one exception. A paragraph describes pubiotomy, "though for all practical purposes this operation has been abandoned in the United States."

Intended as an outline for the medical student and others needing a brief survey of the field of obstetrics, this amply illustrated book is admirably suited to its purpose. Another vital memorial has been added to those of a great teacher, Dr. Jennings Litzenberg.

EUGENE H. COUNTISS

Polycystic Ovaries, Menstrual Disturbances and Hirsutism; Hyperthecosis. By Delamaine A. H. Du Toit. 161 pages with 74 illustrations. Leiden, 1951, H. E. Stenfert Kroese N. V.

This scholarly and consequential thesis is a careful analysis of ten cases of hirsutism associated with polycystic ovaries, and two cases in which the hirsutism had no concomitant ovarian lesion. The author stresses that the term "polycystic ovary" is a purely descriptive one, and does not connote any specific disease entity. Secretions of the cells lining the cyst cavities, and not the size of those cavities, determine the functional significance of such cysts. The etiology of syndromes involving acne, obesity, hirsutism, and amenorrhea may be pluriglandular, and the author rightly emphasizes the necessity for eliminating pathologic conditions of other endocrine organs before incriminating the ovaries. In an extensive critcial review of the so-called Stein-Leventhal syndrome, the author points

out that hirsutism is not an inevitable sequel to theca-cell proliferation and luteinization, so that Stein and Leventhal have not described a true clinical syndrome. The suggestion is made that most cases falling into the category of the Stein-Leventhal syndrome are examples of a polyglandular endocrine disturbance which sets up a vicious circle which can sometimes be broken at more than one point, for instance, by ovarian or adrenal resection. The careful and thoughtful organization of this monograph recommends it highly.

DOUGLAS M. HAYNES

Gesichtspunkte zu Finnischen Gebärerinnenmaterialien (Aspects of Finnish Obstetric Data). By Sirkka Oinonen. 116 pages with 17 illustrations. Helsinki, 1952, Kirjapaino Oy. Liike.

The author has meticulously assembled a staggering aggregate of gross data from the files of the Second Women's Clinic of Helsinki for the years between 1936 and 1945, comparing the external pelvic measurements of pregnant women from northern and eastern Finland with those of pregnant women from western Finland. An attempt is then made to corrleate these data with difficulties encountered during labor and delivery, and the conclusion is reached that women from eastern and northern Finland are obstetrically inferior to women from western Finland. Although this study may have some significance for special students of Finnish antrophology, its interest to American obstetricians is obviously rigorously limited.

DOUGLAS M. HAYNES

Miscellaneous

Sterility, Its Cause and Its Treatment. By J. Jay Rommer, M.D., Gynecological Staff, Beth Israel Hospital, Newark, N. J. 424 pages with 152 illustrations. Springfield, Ill., 1952, Charles C Thomas. $12.50.

The treatise, *Sterility, Its Cause and Its Treatment,* by J. Jay Rommer is very timely in its appearance. The purpose of this publication is very adequately expressed in the preface by Dr. Rommer. Until recently, many attempted to solve the problems of deserving barren couples but relatively few approached the problem either scientifically or systematically. This publication will be particularly valuable in guiding the physician in the systematic investigation and treatment of apparently infertile couples. It will be particularly useful to the general practitioner and the physician "specializing in obstetrics and gynecology" who has not had the benefit of an organized training program, but who is trying to meet the need in a smaller community which does not have the benefit of specialists. This text, being a well-organized concise compendium in semioutline form, will likewise serve both the student and the teacher with a well-organized means of study and teaching. For this reason the reviewer recommends this book for every physician who has the slightest interest in sterility or infertility.

The text itself is well written, brief, to the point, and well organized. In general, the methods, opinions, and treatments are acceptable. Those opinions which are controversial are usually set apart as such.

The topics are discussed in orderly manner. The second chapter, "Physiology of Coitus, Orgasm, Libido and Fertilization," affords most interesting reading but I question the actual importance of some of the physiological functions.

The illustrations are certainly no attempt at masterpieces of art, but they serve their purpose; they are simple, clear, and descriptive. The laboratory and office procedures are complete though the descriptions of these procedures are brief.

The complete references will serve as a wonderful index for those interested in further study or fuller monographs on a given topic.

Since it is variously stated that the fault lies in the male in from 35 to 48 per cent of the cases, and in the reviewer's own practice the male factor accounts for over 40 per

cent of the barren couples, constructive criticism suggests that more time and space be given to the infertile male.

Again I agree with the author in his statement that there is a real need and a great demand for a Bona fide specialty in sterility.

In view of the fact that most physicians doing this work either do not have or will not take the time to manage the case adequately, I sincerely hope that this is the beginning of a new specialty.

OREN R. DEPP

Roentgenology in Obstetrics and Gynecology. By William Snow, M.D. Second edition. 363 pages with 273 illustrations. Springfield, Ill., 1952, Charles C Thomas. $10.50.

This very excellent book, *Roentgenology in Obstetrics and Gynecology,* larger than the first edition and more complete, mirrors the wide experience and perfect technique of the author in presenting a veritable atlas of roentgenograms concerning the practice of obstetrics and gynecology. Throughout the text, the author emphasizes his original observations and personal experiences, and adds the theoretical considerations in such a manner that oftentimes he answers many of the problems with which obstetricians and gynecologists are faced daily.

At the onset, a technique of roentgen study of pregnancy serves well to set the stage, from a historical standpoint, in which the author gives full credit to the many workers in the past who have brought this science up to its present high level of efficiency. Because of the popularity today of the use of roentgenograms to obtain information, which is merely guesswork in many instances, from a clinical standpoint, this text serves a real purpose in pointing out the meticulous application necessary to produce desired accuracy in results as well as those variations which should be understood before any obstetrician accepts findings purely on their own merits.

The discussion of pelvic architecture includes many examples of the variations in pelvic types shown beautifully with roentgenograms. Some of the answers to the causes of difficult engagement and difficulty at the midplane are developed by depicting the important variations of pelvic configuration.

From this discussion one can readily obtain an explanation why there exists, in some circles, the present disbelief or misunderstanding in regard to the interpretation and value of pelvic roentgenograms.

A generous section is given to the study of the fetus in utero, as well as neonatal plates depicting fetal abnormalities.

Soft tissue techniques are adequately discussed, as well as methods of obtaining accurate appraisal of placental implantation. Sections on uterosalpingography, the internal genitals, the urinary tract, and the gastrointestinal tract, with a final review of growths in the pelvis, complete the text.

For both the specialist and nonspecialist alike this book is highly recommended, and should serve its purpose well.

The author himself humbly anticipates this in his dedication, "to the betterment of mankind."

ISADORE DYER

Carbohydrate Metabolism: A Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease. Edited by Victor A. Najjar, Department of Pediatrics, Johns Hopkins University Medical School. 134 pages with 32 illustrations. Baltimore, 1952, The Johns Hopkins Press.

Carbohydrate Metabolism is a symposium in which the recent advances in carbohydrate chemistry are presented and applications made to clinical problems in pediatrics. There are five papers on biochemical topics, each presented by an authority who has done outstanding work in the particular field. Three papers by pediatric authorities present clinical case material and outline rational therapy based on the fundamental research.

The topics discussed can be divided into three general fields: (1) The enzyme systems involved in the synthesis and breakdown of glycogen, and the clinical picture and specific biochemical defects in glycogen storage diseases. (2) The effects of hormonal balance on carbohydrate utilization, and the relation of this to the syndrome of spontaneous hypoglycemia. (3) The interrelation of electrolyte patterns and carbohydrate metabolism, and the management of electrolyte disturbances in diabetic acidosis.

In an excellent summary, the editor correlates the biochemical and clinical presentations and emphasizes how the clinical picture can be defined and clarified in the light of recent advances in fundamental research.

The symposium accomplishes its stated purpose of presenting newer knowledge in this field in a manner which the clinician can understand and in applying this knowledge to specific clinical problems. While the case material is primarily pediatric, the applications will be of value to any physician managing metabolic problems. The individual papers are followed by pertinent bibliographies, and there is a good index.

FRANK DITURI

Les Frottis Vaginaux Endocriniens. By J. Paul Pundel, Agrégé de l'Enseignement Supérieur, with the collaboration de R. Vokaer and de Z. Jaworski. Second edition. 493 pages with 124 figures, and 10 color plates. Paris, 1952, Masson et Cie.

This book, *Les Frottis Vaginaux Endocriniens,* was primarily intended for members of the French medical profession. Admittedly the publications of Papanicolaou, Traut, and Schorr and other American followers have satisfied the requirements of books on the vaginal smear. But the book by Pundel is so well written and organized, the subject matter so clearly presented, its clinical indications and applications so logically and acceptably outlined, as to make it highly desirable reading by anyone in other countries who is conversant with the French language.

The theoretical principles are fully covered in this book and suggestions for practical use in the determination of endocrine deficiency or adequacy and correct therapeutic hormonal correctives are all clearly outlined. Pundel's original contributions on the influence of sex hormones on the vagina, herein contained, are not the least valuable features of the book. These are especially intended to help the physician and gynecologist in everyday clinical practice. It should be noted, however, that the text is one to be studied carefully, and that even the gynecologist who has special interest in the hormonal aspects of his patients, with particular reference to sterility, will need a great deal of time, study, and training to master the techniques of staining of the vaginal smear and its proper interpretation.

There is no doubt that when the specialist applies himself to all aspects of this particular method he will be in a more favorable position to help his patients by clearing up many obscure points revealed in the cytological investigation.

In the field of cancer diagnosis, the task is somewhat simpler, as it is only a matter of morphologic interpretation without reference to hormonal correlations. In either case, the work is too specialized and detailed for the average practitioner or gynecologist. However, for any physician who is deeply interested enough to pursue this study, it can prove a highly rewarding experience.

I. C. RUBIN

Books Received

Certain of these books will be selected for review in the near future:

TITLE	AUTHOR	PUBLISHER
Blood Sugar of Newborn Infants	Jorgen Pedersen	Danish Science, Publisher. Press L & D, Copenhagen
Obstetrica Practica Version	Juan Lean	El Ateneo, Florida 340, 1952. Buenos Aires. 96 ills.
Physiological Changes in Plasma Proteins Characteristic of Human Reproduction	L. G. Macy and H. C. Mack	Childrens Fund of Michigan 600 Frederick St., Detroit, Mich.
Das Inselsystem des Pankreas Price $29.70	Helmut Ferner	Georg Thieme, Verlag, Stuttgart, 1952. 54 ills.
Analgesia and Anesthesia in Obstetrics	J. P. Greenhill	Charles C Thomas, Springfield, Ill. 85 pages, 16 ills.
Annales instituti obstetricii et gynecologici Universitatis Helsinkiensis	Ed. Aarno Turunen	Vol. 26
Anurie bei Chromoproteinurie Price $3.50	Hans U. Zollinger	Georg Thieme, Verlag, Stuttgart. 138 pages, 42 ills.
Rontgenuroskopie Price $3.20	Halul G. W. Gunther	Georg Theime, Verlag, Stuttgart, 1952. Agents, Grune & Stratton, Inc., N. Y. 45 pages, 86 ills.
Grundriss der gynakologischen Endokrinologie	Robert Wenner	Benno Schwabe & Co., Verlag, Basel, 1952. 339 pages, 146 ills.
Gynakologische Strahlen therapie Price $6.20	Richard Kurt Kepp	Georg Theime, Verlag, Stuttgart. Agents, Grune & Stratton, Inc., N. Y. 232 pages, 64 ills.
Clinical Obstetrics Price $10.00	Lull and Kimbrough	J. B. Lippincott Company, Philadelphia. 392 ills., 8 color plates.
Handbook of Gynecological Diagnosis Price $12.00	Walter Neuweiler	Grune & Stratton, New York, 1952. 448 pages, 406 ills.
Gynecological and Obstetrical Pathology Price $12.50	Peter A. Herbert	Lea & Febiger, Philadelphia, 1953.
Gynecology Price $22.50	Robert J. Lowrie	Charles C Thomas Springfield, Ill.
Endocrine Treatment in General Practice Price $8.00	Edited by Max A. Goldzieher and Joseph W. Goldzieher	Springer Publishing Co., Inc., New York, 1953.

Correspondence

Pelvic Tuberculosis in Australia

To the Editor:

In the article by Drs. M. Leo Bobrow and James A. Batts published in the JOURNAL of December, 1952 (Vol. 64, No. 6, p. 1242), a statement is made that we estimate the frequency of pelvic tuberculosis in Australia to be 1 per cent. Then follows a criticism said to have been made by Dr. Sharman, that our low figure is due to not having removed sufficient endometrium.

Dr. Sharman lives in Scotland where there is a notoriously high incidence of tuberculosis, and indeed has never enquired from us how we diagnose pelvic tuberculosis in Australia. However, we would like to state that all our patients have a complete curettage of the endometrium under general anaesthesia in the premenstrual phase of the cycle. In addition, first day menstrual blood is examined by culture or by inoculation for tubercle bacilli, and in some cases an emulsified strip of endometrium has been injected into a guinea pig. Our aim is to find the tubercle bacillus wherever possible and not to rely on histological evidence of giant-cell systems located in the endometrium.

In conclusion, it may interest your readers to know that pelvic tuberculosis is now on the increase in Australia, and that this increase is largely found in the refugee or immigrant population from Europe. The Australian Government is at present implementing a large immigration project.

In the Sterility Clinic at The Women's Hospital (Crown Street) Sydney, the combination of a patient with an unpronounceable name and damaged tubes is a signal for a full investigation for pelvic tuberculosis. In the last seven years there have been 2,920 new patients seen at the Clinic, of whom 12, or about one in 240, have presented evidence of tuberculosis. This is an increase on the figure of one in 600 found here before the recent war amongst native-born Australians.

One wonders, for a young and developing race, whether it is not equally important that the new female immigrant be screened for pelvic tuberculosis as well as for the pulmonary lesion.

ALAN GRANT, M.B., B.S., F.R.C.S., L.M., M.R.C.O.G.
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FEB. 16, 1953

Failure to Give Credit to Pioneer Contributions in Obstetrics

To the Editors:

I have observed with considerable displeasure a growing tendency on the part of writers of articles in the field of obstetrics to ignore original references either in the body of their articles or in the bibliography listed at the end. Naturally, my attention has been called to this by the failure of particular authors who have written on subjects which have especially interested me. If one pursues the investigation of this matter, one finds

that it is not only individual authors who are guilty of failure to give credit to preceding contributions, but that finally this evil ramifies to the editors of leading textbooks, who continue the process into the standard reference books on obstetrics.

Specifically, the subjects in which mention of pioneer reporting by this writer has been neglected are: (1) fractured pelvis in obstetrics, (2) vaginal smears in prognosticating disturbances of pregnancy, (3) measurement of pelvic depth, (4) rerupture or double rupture of the membranes. Very recent articles by well-known authors showed apparent unwillingness to give credit in the latter two instances and, in the first topic mentioned, an author was guilty of nothing short of plagiarism. On the other side of the picture, it is gratifying to note the faithfulness with which Greenhill's *Year Book of Obstetrics and Gynecology* reports such contributions for the literature.

Why do such things occur? It certainly cannot be ignorance, for the guilty ones are often the most "erudite." How to explain the apparent and gross failure to give credit where credit is due? Is it a lack of intellectual honesty on the part of medical writers? The thing that troubles me is the possible motive of those who do the ignoring. It is a form of snobbishness. I have seen it in different varieties. I have seen it at medical meetings; it occurs in medical society and medical school teaching appointments. It is an unpleasant feature of our profession. But nowhere is it as distasteful as in our journals and textbooks. One cannot escape the impression that, in American obstetrics, it is not what the scientific contribution is, but rather who made it. In brief, it is the name that counts. This is in no way to be construed as a criticism of the JOURNAL or of its editors. The journals will publish and do publish everything that appears bona fide, no matter who the author. (The periodicals devoted to reviewing the literature, however, are selective.) The complaint is directed against the individual contributor, whose "research" is either incomplete or absent, if one is to judge by mention of relevant pre-existing material. Too often, the frequent contributor who sails along on his reputation is the one most likely to ignore a significant contribution of one of less professional stature.

Editors can do a great deal to eradicate this scientific dishonesty or carelessness. It should be made more difficult to get an article into print. More accurate references should be required. Credit should be insisted upon, and editorial boards should be called upon to take more responsibility in this connection. Obviously, a single editor cannot be expected to police every paper. Perhaps an improvement could be brought about by an innovation in editorial policy, whereby Original Communications would include only original contributions containing new concepts or describing new entities, whereas reviews or studies that do not advance new ideas be contained in a separate section of the journal, such as Case Reports and New Instruments. Furthermore, no article should be given favored space because of the author or his school or association. These are only suggestions, but it is to be hoped that from this letter will emerge a major effort toward an intellectual reawakening in the field of obstetric literature.

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